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SUBDURAL HEMATOMA AND EFFUSION IN INFANTS

Review of Fifty-Five Cases

ARTHUR R. ELVIDGE, M.D.
AND
IRA J. JACKSON, M.D.
MONTREAL, CANADA

THE RELATIVELY high operative mortality of subdural hematomas in infants as compared with adults offers a challenging problem to pediatricians and neurologic surgeons. In the hope of gaining a clearer understanding of subdural hematomas and effusions in infants, it is our purpose to present in this publication an etiologic and clinical pathologic analysis of 55 cases and to show the importance of maintaining an adequate fluid and protein balance as an adjunct to the surgical treatment of this disorder.

REVIEW OF THE LITERATURE

For a rather common condition, subdural hematomas in infants are infrequently reported in the literature. As early as 1877, Huguenin [1] reported that 2.7 per cent of all cases of subdural pachymeningitis (this is the old term for subdural hematoma) observed at autopsy were in children under 1 year of age. However, it was not until about fifty years later that the literature began to contain reports on the clinical picture and management. Other than the large series of 98 cases recorded by Ingraham and Matson (1944) [2] and of 28 by Statten (1948),[3] each of the remaining few reports contains less than a dozen cases.

From the Department of Neurology and Neurosurgery, McGill University, and the Montreal Neurological Institute.

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1. Huguenin, G.: Diseases of the Brain and Its Membranes, in von Ziemssen, H.: Cyclopedia of the Practice of Medicine, New York, William Wood & Company, 1877, vol. 12, p. 407.

2. Ingraham, F. D., and Matson, D. D.: Subdural Hematoma in Infancy, J. Pediat. **24**:1-37, 1944.

3. Statten, T.: Subdural Haematoma in Infancy, Canad. M. A. J. **58**:63-65, 1948.

Cranial trauma, whether it be natal or postnatal, has long been considered one of the main causes for subdural hematoma in infancy and may produce an acutely or chronically ill patient. It is well known that the chronic subdural hematoma, xanthochromic subdural effusion or hygroma may be the result of a minor or insignificant head injury. Such insignificant trauma may well take place during an apparently normal delivery.

The effusions and hematomas are often described as occurring in undernourished infants. Ingraham and Matson stressed this observation by reporting that one third of their patients came from a poor economic environment. Previously, Ingraham and Heyl (1939 [4] stated that this condition occurs more frequently in undernourished children but that in the majority of instances there is a history of trauma. Rosenberg [5] had never seen this condition occur in a healthy, normally developed breast-fed child. These infants often do appear pale and undernourished, but Naffziger and Brown [6] were of the opinion, as we are, that this is the result rather than the cause. The amount of protein and fluid lost in the subdural space is remarkable. Scurvy (Sutherland,[7] Ingraham and Matson [2] and Ford [8]), purpura and congenital syphilis [8] have also been mentioned as possible etiologic factors. Extracranial infection, especially from the ear, has been associated with subdural effusion in infants (Ingraham and Matson [2] and Penfield [9]). Penfield [10] attempted to induce a fluid exudate beneath the dura in dogs by various inflammatory and infectious agents placed on the dura, and little, if any, increase in the subdural fluid was obtained. He reported that the subdural space in dogs contains clear yellow fluid which is distinct from the cerebrospinal fluid.

The great majority of subdural hematomas and effusions are situated over the cerebrum, but Coblentz [11] reported an encysted subdural

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4. Ingraham, F. D., and Heyl, H. L.: Subdural Hematoma in Infancy and Childhood, J. A. M. A. **112**:198-204 (Jan. 21) 1939.

5. Rosenberg, O.: Die Pachymeningitis haemorrhagica interna im Kindesalter, Ergebn. d. inn. Med. u. Kinderh. **20**:549-638, 1921.

6. Naffziger, H. C., and Brown, H. A.: Chronic Subdural Hematoma in Infants, S. Clin. North America **14**:1465-1483, 1934.

7. Sutherland, G. A.: On Hæmatoma of the Dura Mater Associated with Scurvy in Children, Brain **17**:27-36, 1894.

8. Ford, F. R.: Diseases of the Nervous System in Infancy, Childhood and Adolescence, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1946, pp. 918-922.

9. Penfield, W. G.: Subdural Effusion and Internal Hydrocephalus, Am. J. Dis. Child. **26**:383-390 (Oct.) 1923.

10. Penfield, W. G.: The Cranial Subdural Space, Anat. Rec. **28**:173-175, 1924.

11. Coblentz, R. G.: Cerebellar Subdural Haematoma in Infants Two Weeks Old with Secondary Hydrocephalus, Surgery **8**:771-776, 1940.

hematoma overlying the cerebellum in a 2 week old infant and stated that the literature revealed only 4 such cases. Bloody subdural effusion was observed in the posterior fossa in one of our cases.

The treatment has varied from subdural aspiration, followed by a low mortality rate and high incidence of mental retardation by Sherwood,[12] and craniotomies, followed by a high mortality rate and low incidence of mental retardation by Peet and Kahn,[13] to a combination of aspirations, trepanation and craniotomy by Ingraham and Matson.[2] These last authors have outlined a satisfactory treatment based on sound physiologic understanding of the infant.

The patients show a heterogeneous symptomatology, varying from an infant who is not doing well to one with convulsions, hydrocephalus or focal neurologic signs.

For the sake of clarity, we prefer to use the term hematoma in instances when a blood clot was seen within the subdural effusion and the term xanthochromic effusion in those when the color of the fluid varied from yellow to orange brown. The xanthochromia is merely the result of breakdown products of blood. None of the infants reported in this series had colorless subdural effusions.

ETIOLOGIC AND SYMPTOMATOLOGIC ANALYSIS

In approximately the last twelve years subdural hematomas or xanthochromic subdural effusions were shown to be present in 55 infants treated in the Montreal Neurological Institute. We have classified these patients under four etiologic headings, namely, definite birth injuries, probable birth injuries, postnatal head injuries and unclassified causes. With this etiologic classification, the symptomatology and clinical pathologic changes present striking characteristic features within each group and, to some extent, govern the general plan of management.

1. *Group of Definite Birth Injuries.*—The basis for this etiologic group of 10 patients was direct pathologic evidence of cranial birth trauma, as shown by skull fractures in 6 infants and tentorial tears in 3 others.[14] The remaining 5 day old infant had frank subdural bleeding without skull fracture and without evidence of hemorrhagic disease of the newborn. The patients presented histories of difficult labor, instrumental delivery and symptoms referable since birth. At the time of admission to the hospital their average age was 1 to 5 days, while 1 patient was 21 days old.

12. Sherwood, D.: Chronic Subdural Hematoma in Infants, Am. J. Dis. Child. **39**:980-1021 (May) 1930.

13. Peet, M. M., and Kahn, E. A.: Subdural Hematoma in Infants, J. A. M. A. **98**:1851-1856 (May 28) 1932.

14. Tentorial tears were observed at autopsy.

Chase [15] most convincingly pointed out the relationship between tentorial splits and subdural hemorrhage in infants. In 145 autopsies on babies under 4 weeks of age, 50 showed intracranial hemorrhage of which 32 also presented splitting of the tentorium cerebelli. He stated that subdural hemorrhage with splitting of the fibers of the tentorium cerebelli is indisputable evidence of intracranial trauma. He stated his belief that stretching and tearing of tributaries of the great vein of Galen during the process of molding and consequent raising of the vertex of the fetal skull during labor were responsible for supratentorial hemorrhage. Obviously, operative manipulation increases this possibility. The effect of the forces of stress and strain on the fetal head during its passage through the birth canal is well recognized (Beneke,[16] Warwick,[17] Holland,[18] Ehrenfest [19] and Greenwood [20]). Holland showed that the pressure exerted on the fetal head in one diameter results in a shortening in that diameter and a compensatory increase in some other diameter. Therefore it is felt that the causative factor of trauma in our 10 infants is quite definitely established.

These newly born infants presented a uniform clinical picture. After a difficult labor and delivery, they were admitted to the neurosurgical service with the classification of an acute head injury. Spasticity was the most prevalent physical finding on admission to the hospital. Four infants had tense fontanels, while the clinical picture of hydrocephalus was seen only in the 21 day old patient. This is what might be expected, as hydrocephalus takes time to develop. Seizures, focal and generalized, abnormal neurologic findings, such as pupillary signs and extraocular paresis, and respiratory difficulties each occurred in about one third of the babies. Opisthotonos was observed in only 3 of the 10 infants, but statistically it was of greater incidence in this group than in the other three etiologic groups.

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15. Chase, W. H.: An Anatomical Study of Subdural Haemorrhage Associated with Tentorial Splitting in the Newborn, Surg., Gynec. & Obst. **51**:31-41, 1930.

16. Beneke, R.: Ueber Tentoriumzerreissungen bei der Geburt, sowie die Bedeutung der Duraspannung für chronische Gehirnerkrankungen, München. med. Wchnschr. **57**:2125-2127, 1910.

17. Warwick, M.: Necropsy Findings in New-Born Infants, Am. J. Dis. Child. **21**:488-499 (May) 1921.

18. Holland, E. J.: Cranial Stress in the Fœtus During Labour and the Effects of Excessive Stress on the Intracranial Contents, with an Analysis of Eighty-One Cases of Torn Tentorium Cerebelli and Subdural Haemorrhage, J. Obst. & Gynæc. Brit. Emp. **29**:549-571, 1922.

19. Ehrenfest, H.: The Causation of Intracranial Hemorrhages in the New-Born, Am. J. Dis. Child. **26**:503-514 (Dec.) 1923.

20. Greenwood, W. O.: Moulding of the Fœtal Head and Its Consequences, J. Obst. & Gynæc. Brit. Emp. **31**:611-621, 1924.

Treatment was administered shortly after admission to the hospital, consisting of elevation of depressed fractures, trepanation and drainage or craniotomy and evacuation of fluid. Six infants died either immediately after the operation or during the first postoperative day, yielding an alarming operative mortality rate of 60 per cent. Of the 4 infants who survived operation, 2 were treated by trepanation and drainage and 2 by craniotomy.

A striking observation in these infants was the high (90 per cent) incidence of bloody subdural fluid. In only 1 instance was clotted blood seen. The single case of xanthochromic effusion was that of the 3 week old infant who was brought to hospital because of an enlarged head, and roentgenograms of the skull revealed a linear fracture. In contrast to the other groups of patients, no subdural membrane was found. In 1 instance the bloody subdural effusion was seen in the posterior fossa. Bilateral effusions were observed in 8 patients.

The observations at autopsy were most significant in explaining the high mortality rate. Diffuse subdural and subarachnoid hemorrhages were seen in 2 babies, pericardial and pleural hemorrhages in another 2 babies and tentorial hemorrhages in 3. One baby's condition was diagnosed as hemorrhagic disease of the newborn.

A nine and ten year follow-up study on 2 survivors treated by trepanation revealed normally developed children who have done well in school and at home and have no abnormal neurologic signs. Only 1 infant who underwent craniotomy was able to be followed and at 1 year of age presented a mentally and physically retarded child with seizures.

2. *Group of Probable Birth Injuries.*—The etiologic classification of probable birth injuries was established because 26 patients presented only indirect but most suggestive evidence of an intracranial birth injury. These children differed from the previous group in that they were admitted to the hospital at an older age and as chronically ill patients. The ages ranged from 13 days to 14 months, with an average of 5.34 months.

Fourteen patients presented a history of a difficult labor and instrumental delivery; 11 presented signs and symptoms recognizable since birth and 3 were born prematurely. It is interesting to note that 20 per cent of these patients were born as a twin. The trauma that can be created at birth by a difficult labor or instrumental delivery has already been mentioned.

The fact that the symptomatology of some of the infants in this group had been present since birth would most likely indicate that they had sustained a cerebral injury at birth, in spite of the absence of a history of a difficult labor or delivery. Naffziger and Brown [6] reported

that there was usually lacking a definite history of trauma in chronic subdural hematomas in infants but that it seemed possible that the molding of the head and movements of the bone along the suture line might be sufficient to produce a tear of the pial veins.

Chase [15] stated that prematurity is the most important predisposing factor in intracranial hemorrhage, as well as tentorial splitting in the infant. He showed the fibrous connective tissue of the premature infant to be immature, thereby indicating increased friability and vascularity of the tentorium, whereas in the full term infant the tentorium is relatively avascular. Therefore it was felt that the causative factor of trauma in the production of subdural effusion in these 26 infants was indirectly established.

These infants were admitted to the hospital as chronically ill patients. The great majority were brought to the hospital because of an enlarged head. On examination all infants in this group had hydrocephalus. The second major reason for hospitalization was seizures. Sixteen infants had a history of convulsions as part of their present illness.

Five patients exhibited spasticity and 2 opisthotonos. One half of the patients had a history of taking their feedings poorly before coming to the hospital. Seven infants (26 per cent of this group) had a history of respiratory difficulties which usually occurred during only the first week of life.

Other abnormal neurologic findings consisted of hyperactive deep tendon reflexes and absent abdominal reflexes in 3 patients; a slight hemiparesis in 1 of these; a paresis of the extraocular muscles in 4; facial paresis in 1, and unequal pupils and a constant nystagmus in another. Two infants had a history of transient hemiparesis after birth. These 11 infants had bilateral effusions. Therefore, the abnormal neurologic findings were of no localizing value. Six infants had evidence of extracranial infection, which was an otitis media, either during the onset of their present illness or on admission.

The operative treatment consisted of subdural taps, trepanation with or without drainage and, when necessary, craniotomy.

Bilateral subdural effusions were observed in 19 patients and unilateral effusions in 7. In those with bilateral effusions, the character of the subdural fluid—that is, bloody or xanthochromic—was the same on both sides with the exception of 1. In other instances in which the treatment was carried out by means of repeated subdural taps, it was not uncommon to see the bloody fluid become xanthochromic within less than a month.

Xanthochromic fluid was found on admission in 18 infants, of whom 14 had bilateral effusions and 4 unilateral effusions. Bloody fluid was obtained in 8 patients, of whom 5 had bilateral effusions and 3

the unilateral type. The protein value of the xanthochromic fluid ranged from 148 to 3,390 mg. per hundred cubic centimeters. In some instances the bloody subdural fluid had a protein value comparable to that of blood—around 6,000 mg. per hundred cubic centimeters. The significance of these high protein values will be discussed in the following section.

Blood clots were seen within the effusion in only 4 patients. Subdural membranes were observed in 24 instances in 15 patients, of which 9 in 5 patients were encapsulated bloody effusions.

The spinal fluid from 7 infants was clear and colorless and contained a normal amount of protein. Two patients had yellow spinal fluid with an elevated protein value, and the 15 day old infant had bloody fluid.

Five infants died following operation, yielding an operative mortality of 19.2 per cent (2 of immediate postoperative shock; 1 of generalized cerebral damage; 1 of purulent pericarditis, and 1 of status epilepticus). One patient in this group with a bilateral bloody effusion died during his stay in the hospital but was not included as an operative mortality because the cause of death was a subdural abscess which was found on entry to the hospital.

Fourteen infants have been followed for periods of six months to six years. Seven have had normal development after operation (1 following subdural taps, 4 following trepanation and drainage and 2 following craniotomy and drainage), with no enlargement of the head or abnormal neurologic signs. Seven infants seen at six to thirty months after operation (2 after subdural taps, 4 after trepanation [21] and drainage and 1 after craniotomy) showed mental retardation and some neurologic deficit.

3. *Groups with Postnatal Head Injuries.*—The third group of the etiologic classification of subdural effusions is comprised of patients whose complaints definitely followed a severe postnatal head injury. The 9 patients in this group were reported to be in good health before their accident. Their ages ranged from 2 months to 30 months, with an average of almost 14 months. Six were admitted to the hospital in a state of unconsciousness shortly after their accident. The other 3 patients were brought to the hospital in a conscious condition two to six weeks after a definite head injury. Therefore the etiologic factor of postnatal trauma seems most definite in this group.

They presented much the same clinical picture as an adult would following a severe head injury. Hemiparesis, reflex changes, spasticity,

21. One of these infants had subdural empyema postoperatively, was seen 1 year after operation and showed decided mental retardation.

respiratory difficulties, restlessness, unconsciousness, shock and a history of a recent head injury were the predominent observations. Their general condition was acute, and the treatment for shock was instituted on admission.

Six unconscious infants underwent operation soon after being admitted to the hospital (trepanation and drainage in 3 and craniotomy and drainage in 3). In all instances the subdural fluid was bloody, and blood clots were discovered in 5 infants. Two effusions were bilateral and 4 were unilateral. One infant received a lumbar puncture on admission which revealed the spinal fluid to be bloody and under increased pressure. These 6 infants died within twelve hours after operation. The autopsy observations revealed, in addition to the known subdural and subarachnoid hemorrhages and skull fractures, laceration of the brain.

The other 3 patients in this group came to the hospital two to six weeks after their head injury as chronically ill infants. Their complaints definitely followed their head injury, as evidenced by a history of unconsciousness in 2 and a skull fracture in the third. This last child began to have focal cortical seizures and feeding difficulties a week after its accident.

One infant was seen two years after treatment by trepanation, presenting no evidence of mental retardation and only a slight hemiparesis.

Therefore, in this group with postnatal head injuries, 3 infants had roentgenographic evidence of a skull fracture, 8 had bloody effusions of which 2 were bilateral and 1 had bilateral xanthochromic effusion. The operative mortality was 77.7 per cent. Thus it seems that the clinical pathologic observations in this group of infants are quite similar to those seen in the adult with acute subdural hematoma.

4. *Unclassified Group.*—These 10 infants with subdural effusions are grouped as unclassified because there was no history of a difficult labor, instrumental delivery, prematurity, symptomatology since birth or postnatal head injury. The ages at the time of admission to the hospital ranged from 2 to 24 months, with an average age of 12.5 months. These infants were brought to the hospital as chronically ill patients and represent 17.8 per cent of this series. Perhaps the reason for the existence of this etiologic group is the lack of pertinent facts obtained in the history from the parents. Ingraham and Matson [2] stressed the point that these histories are often inadequate and incomplete. The comparison of signs and symptoms and clinical pathologic changes in this group of patients and those in the group with probable birth injuries and postnatal head injuries reveals many striking similarities—some so striking that with a more adequate history there

might not have been an unclassified group. There was no roentgenographic evidence of vitamin deficiency, nor were blood dyscrasias noted from hematologic smears. Ford [8] stated the average age for the onset of appearance of scurvy is 4 to 18 months.

On admission to the hospital these infants, with the exception of 1, presented much the same clinical picture as did the patients with the probable birth injury or the chronically ill infants with the postnatal injury. Eight of the group were brought to the hospital either because of an enlarged head or because of seizures. Hydrocephalus, seizures and paresis were the most prevalent signs. Three infants had papilledema, a symptom observed in only 1 other in the entire series (a child in the group with postnatal head injuries). This is the only group in which opisthotonos was not observed. Six infants had extracranial infection (otitis media, 4; pneumonia, 1; meningitis, 1) coincident with the onset of their seizures or paresis. The onset of the symptoms, as far as could be ascertained from the histories, ranged from two days to sixteen months before admission to the hospital, with an average of six months.

The treatment consisted of subdural taps, trepanation and drainage and craniotomy.

Bilateral subdural effusions were seen in 7 infants. Bloody fluid was observed in 2 patients. Protein values of 525 to 4,120 mg. per hundred cubic centimeters were reported on the subdural fluid of 2 patients. A subdural membrane was found in 4 patients. Five infants had one or more lumbar punctures performed, and in all instances but one the fluid was clear and colorless with normal protein values. The one abnormal spinal fluid contained 48 mg. of total protein per hundred cubic centimeters.

Two patients died after operation of shock, yielding an operative mortality of 20 per cent. In 1 who died on the first postoperative day, continous closed drainage of the subdural space was instituted, and it was thought the large amount of fluid lost in this manner was responsible for his death.

Therefore, even though no history could be obtained referable to a head injury, either natal or postnatal, these infants presented a clinical picture similar to that of the infants with chronic subdural effusion as a result of probable birth injury or of postnatal head injury seen weeks after the original trauma.

Four patients were followed for one to three years. Three showed no evidence of mental retardation (1 after subdural aspiration, 1 after trepanation and 1 after craniotomy). The one who underwent only subdural aspiration did have a minimal residual hemiparesis and died three years later of congenital heart disease. The fourth infant was mentally and physically retarded one year after subdural aspirations.

DIAGNOSIS

1. *Clinical Picture.*—Any infant with hydrocephalus or seizures should be suspected of having a subdural effusion. When the infant's state of consciousness is disturbed and there are abnormal neurologic findings present following a recent head injury, whether it is natal or postnatal, the diagnosis of subdural effusion becomes more obvious. Other than the characteristic symptoms and physical signs already given, some of these patients also exhibited vomiting, malaise, hyperthermia and drowsiness; but these findings were not sufficient to be of statistical value in the diagnosis of subdural effusion.

2. *Subdural Puncture.*—The only positive method of diagnosing a subdural effusion without direct visualization is by subdural puncture. In most instances these punctures should be made at the lateral angles of the anterior fontanel. In order to minimize subsequent leakage of subdural fluid through the skin, a short, sharp, bevelled no. 18 lumbar puncture needle should be inserted obliquely from layer to layer, finally puncturing the dura. As supratentorial subdural hemorrhage may arise from tearing of tributaries of the great vein of Galen, puncture posteriorly through the lamboid suture may be desirable in some of the very young infants. The anterior fontanel, however, appears to be the most practical site for puncture in the average child. If colored fluid is not immediately obtained, aspiration should not be carried out because cortex is so easily aspirated in such circumstances. Slowly dripping clear fluid generally indicates that the point of the needle is in the subarachnoid space. If a high degree of internal hydrocephalus is present, the needle may have entered the ventricle, as the cortex is extremely thin in such patients.

The presence of bloody fluid is indication of recent hemorrhage, while xanthochromic fluid is evidence of old hemorrhage. The xanthochromia is due to bilirubin or like pigment derived from heme, which is a breakdown product of blood. Protein determinations of this fluid should be carried out, with the amount removed noted. These figures give an index of the actual amount of protein lost and thereby guide one in the systemic administration of protein and fluid, as will be discussed in the following section. Bloody collections contained as much as 6,000 mg. of total protein per hundred cubic centimeters and xanthochromic fluids as much as 3,000 mg. It is remarkable that in the face of the high protein content of the subdural fluid the subarachnoid fluid may retain a normal value of protein unless taken shortly after a head injury, when the value might be elevated.

3. *Roentgenologic Examination.*—Roentgenograms of the skull may reveal evidence of a fracture or separation of the suture lines, depending on the circumstances.

4. *Pneumography.*—In the case of the hydrocephalic infant, pneumography is of special value in the diagnosis of the degree and type of hydrocephalus and of the existence of subdural effusion (figs. 1, 2 and 3). It is useful after an operative procedure in order to estimate the amount, if any, of residue in the subdural space, to determine a shift of midline structures or to follow the degree of ventricular dilatation or cerebral atrophy (fig. 4). If ventricular dilatation and increased pressure exist, ventriculography by way of the anterior fontanel is the

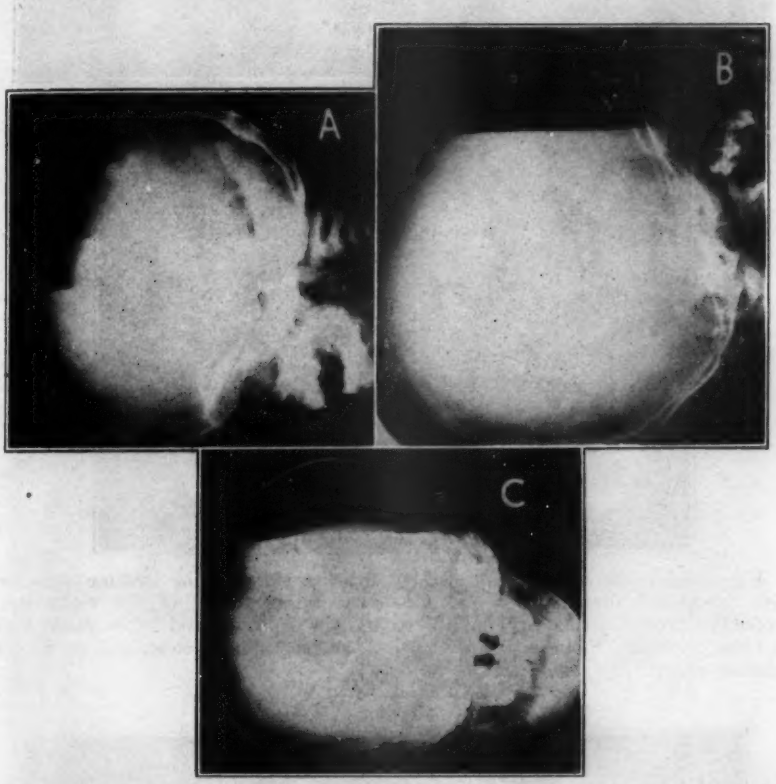

Fig. 1.—Air and fluid levels seen in the subdural space caused by subdural replacement of oxygen. *A*, brow down lateral view, showing in addition displacement of the brain away from the inner table of the skull. *B*, brow up lateral view. *C*, anteroposterior projection with right side dependent.

method of choice. If the infant is small, it is inadvisable to do a ventricular puncture because of the possibility of producing unnecessary damage to the brain. An encephalogram is difficult to make and may be dangerous if an abnormal increase in intracranial pressure exists. However, it may be justifiable when brain pressure is not high in order to determine the amount of residual displacement or in diagnosis in a complicated case. Roentgenograms of the skull and oxygen studies are then of value for obvious reasons.

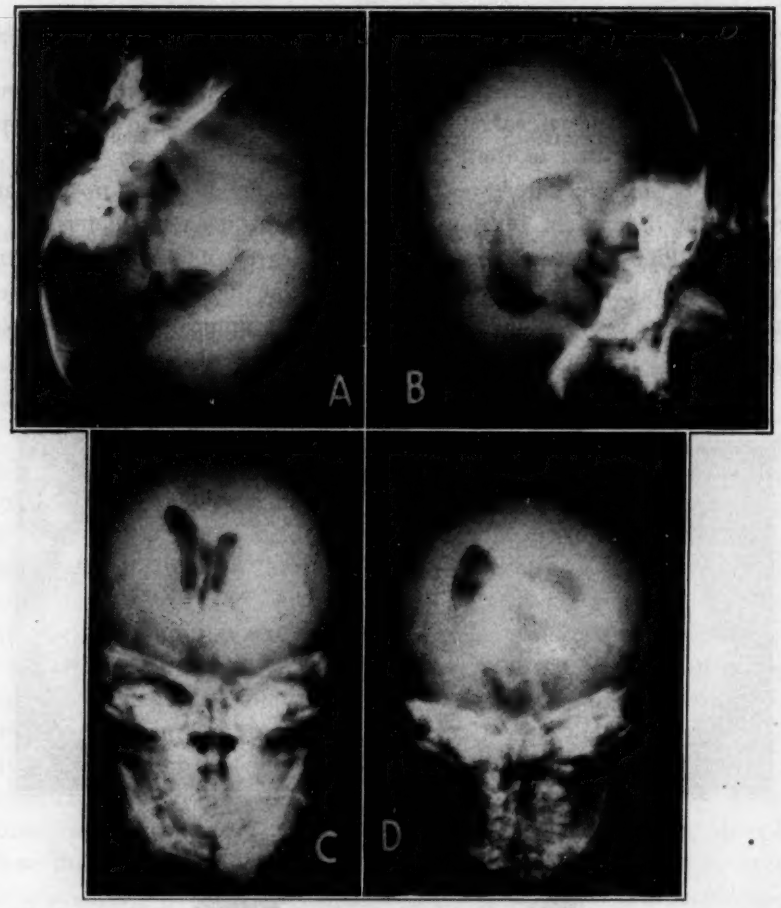

Fig. 2.—Unilateral subdural effusion causing shift of the midline structures, with downward displacement and a smooth filling defect of the right lateral ventricle. Note shifting of subdural oxygen in brow up and brow down views. *A*, brow up view; *B*, brow down view; *C*, anteroposterior view, and *D*, posteroanterior view.

Fig. 3.—Bilateral subdural effusions in 2 patients. Posteroanterior views showing displacement of the cerebral cortex from the inner table of the skull on both sides. There is no shift of the midline structures.

In order to gain a greater appreciation of the pneumographic findings in these patients, perhaps a few statements in regard to hydrocephalus will help.

The term internal hydrocephalus merely denotes a condition set up as a result of a block to the intracranial circulation of cerebrospinal fluid. Such a block may occur within the ventricular system, resulting in a noncommunicating type of internal hydrocephalus. However, if

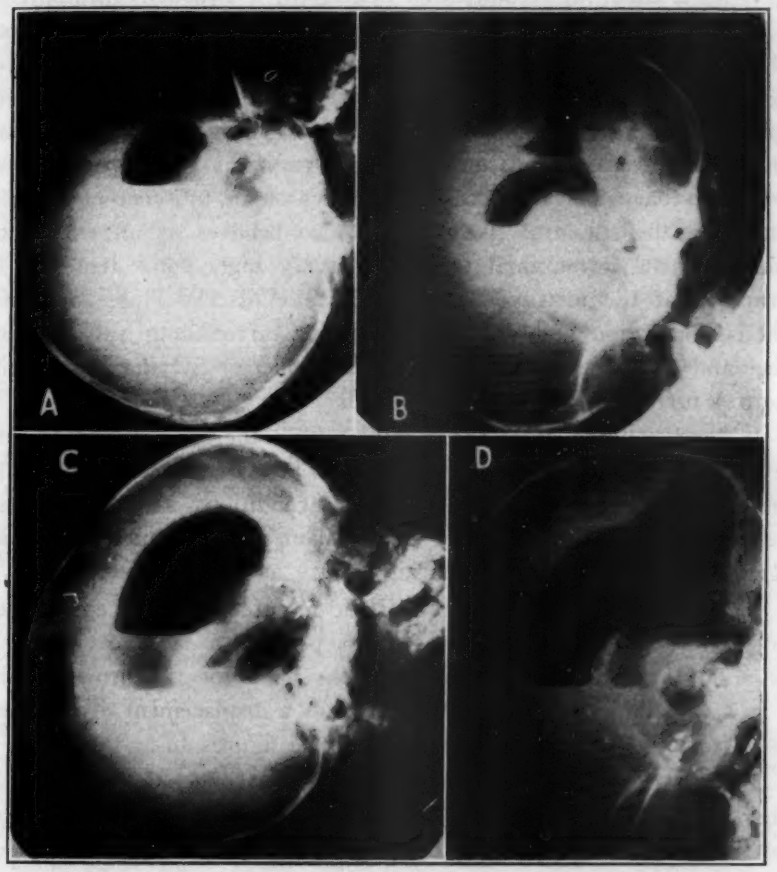

Fig. 4.—Preoperative and postoperative roentgenograms taken three months apart. *A* and *B* are preoperative brow up and brow down views, showing subdural air and fluid in change of position and asymmetric dilatation of the lateral ventricles. *C* and *D* are postoperative brow up and brow down views showing dilatation and asymmetry of the lateral ventricles. The silver clips outline the bone flap.

the subarachnoid space is blocked, a communicating variety of internal hydrocephalus occurs.

A subdural effusion may be classified under the general term hydrocephalus, which merely signifies a condition of excessive fluid

within the cranial cavity. Since subdural fluid is trapped outside the channel of the cerebrospinal fluid circulation proper, it may be described as an external type of hydrocephalus, which is generally agreed to be a poor term, a condition which has been rather ill defined in the literature. A loculation of fluid in the subarachnoid space separated from the cerebrospinal fluid circulation probably could also be so designated.

When a subdural accumulation is present, it is usually widespread. It causes a compression of the surface of the hemisphere and may obliterate the local subarachnoid channels. If sufficient reduction of the cerebrospinal fluid pathway results, a secondary internal hydrocephalus of the communicating variety arises. Thus, progressive enlargement of the head and pressure symptoms are apparent over and above that which may occur as a result of the presence of the new volume in the subdural space, which also behaves as an expanding lesion. If the intracranial pressure is very high, some tendency to herniation at the incisura tentorii may take place. This may cause venous congestion and obliteration of the surrounding subarachnoid space and possibly a narrowing of the aqueduct of Sylvius, thus giving rise to a further degree of hydrocephalus.

In long-standing cases the volume within the subdural space may remain relatively unaltered. The brain and the circulation of the cerebrospinal fluid may adjust to the new conditions. The intracranial pressure gradually may become and remain normal, unless a physiologic or pathologic stress or strain occurs at a later date.

There is apparently no characteristic feature in the encephalogram for subdural effusion in infants, unless perhaps a fluid level seen in the subdural space when positioning the head for the brow up and brow down films (figs. 1 and 4*a* and *b*) or a displacement of the brain away from the inner table of the skull, e. g., figures 1*a* and 3.

If the effusion is unilateral or greater on one side than on the other, there will be seen a shift of the midline structures away from the side of the lesion. In a unilateral effusion, one may see, in addition to the aforementioned signs, a smooth filling defect in the ventricular system (fig. 2). The pneumographic findings of bilateral effusion of almost equal size present a communicating hydrocephalus with no shift of the midline structures and displacement away from the inner table (fig. 3).

5. *Electroencephalography.* — Electroencephalography may be of interest but is not necessary in the diagnosis. As a rule, the patients are too young for its satisfactory employment.

TREATMENT

A. Surgical Methods of Treatment.—1. Subdural Aspiration: The simplest method of treatment is aspiration of the subdural space as described under the section on diagnosis. No anesthetization is necessary. However, aspiration generally has to be repeated, which unfortunately means that an intermittent emptying and filling process is going on. This results in loss of fluid and protein as described in the following section. Furthermore, if a well formed inner membrane is present, this will still prevent expansion of the brain and obliteration of the subdural space. Sherwood [12] reported on 9 patients who were all treated by subdural puncture and aspiration of the fluid. His mortality rate was quite low, but his incidence of mental retardation was high. However, subdural taps do have an important place in the treatment of subdural effusions. Ingraham and Matson [2] carried out subdural taps daily, alternating sides for about one to two weeks, removing small amounts each day and, in the meanwhile, building up the patient's general condition for further procedures as trepanation and craniotomy. We believe that subdural taps can be used as the treatment in the acute subdural hemorrhage in which the blood to be aspirated from the subdural space is fresh and unclotted. This is especially true in the newborn infant. Occasionally, a single aspiration is sufficient. When these infants are trephined, usually no membrane is found. After a week or so of aspirations, an encephalogram may be carried out in order to see whether or not the brain has expanded and the dead space been obliterated.

2. Trepanation: Trepanation of the skull with the patient under general anesthesia is indicated if the brain has not expanded and the pressure remains elevated and, most important of all, for identification of subdural membranes under direct vision. If no membranes are found, the subdural space may be drained for one to five days, during which time strict asepis must be maintained in order to avoid infection. This should give a more even evacuation of fluid than is obtained by intermittent aspiration and in the absence of an inner membrane may be alone successful. If an inner membrane is found, the wound is closed with or without drainage and the patient is prepared for a craniotomy within a week. More recently, we have preferred to complete the craniotomy (osteoplastic or free) on the same day after verification of membranes, using the burr opening as the point of origin of the craniotomy. The inner membrane cannot be adequately disrupted through such a small exposure to effect satisfactory expansion of the brain. The frontal and occipital pole can be visualized through the midparietal flap. A thin transparent membrane may easily be overlooked.

3. Craniotomy: Osteoplastic craniotomy and removal of the membranous sac have to be classified as a major procedure. It has been expressed by Ingraham and Matson [2] that the best results may be obtained by preliminary subdural punctures followed by trepanation and, finally, by osteoplastic craniotomy with removal or disintegration of the membrane. However, they remove the membrane only to a point just beyond the edge of the bone flap. This regimen seems to be a safe over-all method of treatment and has given most excellent results in their hands. Peet and Kahn [13] reported a mortality rate of more than 50 per cent in 9 infants following craniotomy but a low incidence of mental retardation. We wish to emphasize, however, that it is essential to remove the whole of the inner membrane, which may extend from the frontal to the occipital poles. This removal can be

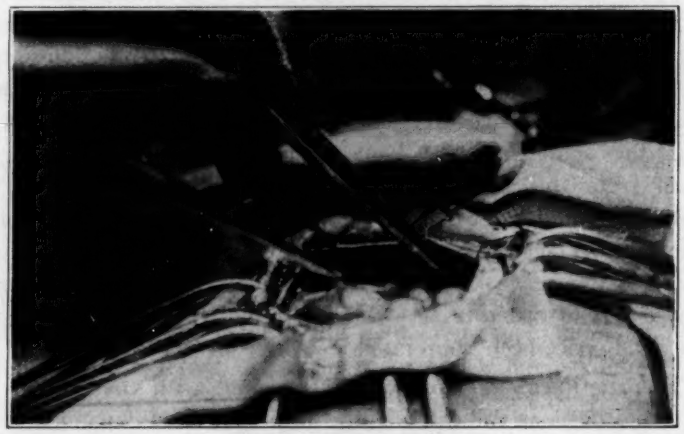

Fig. 5.—Photograph showing a thin subdural membrane at operation. Note the large space between the dura and brain. This membrane extended from the tip of the frontal pole to the occipital pole.

done through the same opening. Without the removal of the inner membrane, certain portions of the brain will not be able to expand (fig. 5).

Craniotomy and removal of membranes in infants are attended with considerable shock because of the sudden evacuation of the dead space which will fill up with protein-containing fluid if the brain does not expand rapidly to collapse the defect. Naffziger and Brown [6] stated that these infants poorly tolerated the release of large quantities of subdural fluid. It is not unusual to see an infant become ashen gray following the aspiration of 50 cc. of fluid.

In an attempt to aid the expanding brain and effect closure of the dead space, we occasionally inject at the close of the operative exposure a limited quantity of a modified Ringer's solution through

the lumbar subarachnoid space. The pressure is raised sufficiently in the ventricles, generally more than in the subarachnoid space, so that the subdural space collapses. Ventricular injections, of course, can be used to build up the pressure, but frequently the fluid will leak through the needle tract, and we prefer to avoid punctures through the hemisphere unless absolutely necessary. Sometimes the injected material escapes via the subarachnoid space and is only partly effectual. Convulsions will occur if the expansion is carried out too rapidly. Oxygen was first used for this purpose by Cone [22] but was replaced by modified Ringer's solution because of the less irritating effect on the subarachnoid lining. If the dead space is small or if the brain is seen to be expanding satisfactorily, the lumbar injections are not necessary.

In infants the relief of intracranial presure causes the suture lines to collapse and the intracranial space is immediately reduced. The inner membrane must be removed, otherwise the brain cannot expand and it remains permanently constricted. It is this feature which is responsible in most instances for the mental retardation seen in these infants years later. The brain does not have a chance to grow because of the restricting effects of this inner membrane.

One baby was treated by repeated aspirations but finally died in a state of inanition. Intracranial pressure had not been high. Fluid and protein intake had been adequate. At autopsy it was seen that heavy membranes covering the entire brain had obviously kept it from expanding. The actual cause of death was not discovered. However, it seemed to be related in any case to the general inability of the brain to expand as a result of a dense inner membrane wholly enveloping the brain, including the base. Thus, the question arises whether its failure to gain weight was due to central causes. The question of fluid and protein loss as a result of repeated subdural punctures will be discussed under the section on fluid and protein balance.

4. Continuous Closed Drainage: One of us (A. R. E.) has employed a system of continuous closed drainage in the treatment of subdural effusion without inner membrane (fig. 6). Though this procedure is effectual in collapsing the subdural space, we consider it a dangerous method. The subdural space is emptied by continuous slow drainage and provides through constantly controlled negative pressure the possibility of fairly rapid closure of the subdural space, especially in stubborn cases. The disadvantages and dangers, however, are many. The drainage must not be too rapid, for the great loss of fluid and protein must be cared for simultaneously. Epileptic attacks may be precipitated by the rather rapid expansion of the brain. Strict

22. Cone, W. V.: Personal communication to the authors.

asepsis must be maintained during the continuous drainage, for infection is a real danger. The continuous drainage should be made to run slow enough that the relative obliteration of the subdural space will gradually occur and be maintained by the normal physiologic adjustments. The advantage of the method is that it will collapse the space rapidly and avoid the intermittent emptying, filling and shifting of the brain by frequent subdural punctures.

B. *Supportive Measures in Treatment.*—We believe that the failure to understand and maintain adequate fluid and protein balance in infants with subdural effusions is greatly responsible for the high operative mortality experienced by many neurologic surgeons. The protein lost in the subdural space is considerable. The values range from 300 to

Fig. 6.—System of continuous closed drainage.

6,000 mg. per hundred cubic centimeters. The effect of this lost protein is twofold—it no longer can be utilized for body needs, and it attracts extracellular fluid from outside the subdural space. Therefore, an infant whose nutritional reserves are so limited during the first few years of life is slowly losing protein and fluid which are not provided by a normal diet.

Protein values of 3,000 to 6,000 mg. per hundred cubic centimeters are usually demonstrated for the bloody effusions. The xanthochromic subdural effusion, which contains from 300 to 3,000 mg. of total protein, is the result of the degenerated breakdown products of a bloody subdural effusion or hematoma. When blood is present in an abnormal habitat, such as the subdural space, it begins to undergo degeneration. One of its main breakdown products is bilirubin, which is derived

from the heme fraction of hemoglobin. It is bilirubin, or a bilirubin-like pigment, that is responsible for the xanthochromia.

It is well known that subdural effusions may increase in size during the months following the original injury. An adequate explanation for this was offered by Gardner,[23] who placed blood in a cellophane® sac surrounded by cerebrospinal fluid. The sac increased in weight, and he felt this indicated that the neomembrane is permeable to fluid but not to protein molecules, and that an osmotic imbalance exists in favor of the contents of the cyst. Zollinger and Gross [24] were of the opinion that the blood within the subdural hematoma slowly breaks down within a few months; the disintegration of blood increases the osmotic pressure, and the blood is diluted. This seems most reasonable, as degenerated blood per se contains 15 to 20 Gm. of total protein per hundred cubic centimeters (Jackson [25]), while usually only several grams per hundred cubic centimeters are present in the chronic hematoma or xanthrochromic effusion. The progression of symptoms and findings indicates enlargement of the subdural contents due to attraction of extracellular fluid as a result of osmosis. However, in some instances a curious situation has been observed by us in that the protein content itself of fluid from repeated aspirations increased rather than decreased or remained more or less constant. This suggests the possibility that molecules of serum protein are added by way of exudation through vessel walls. These observations do not necessarily contradict Gardner's hypothesis, but it does seem possible that neomembranes may not be completely impermeable to protein molecules. Nevertheless, the osmotic pressure is still greater within the sac.

Dandy [26] and Wycis,[27] in discussing hygromas in adults, attributed colorless and xanthochromic subdural collections to a ball-valve-like opening in the arachnoid. If the hygromas were due merely to stagnant collections of cerebrospinal fluid, one would hardly expect to find such high protein values. It is conceded, of course, that collections of non-pigmented fluid in the subdural space may so result, but none of the present cases is of this type.

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23. Gardner, W. J.: Traumatic Subdural Hematoma, with Particular Reference to the Latent Interval, Arch. Neurol. & Psychiat. **27**:847-858 (April) 1932.

24. Zollinger, R., and Gross, R. E.: Traumatic Subdural Hematoma: Explanation of Late Onset of Pressure Symptoms, J. A. M. A. **103**:245-249 (July 28) 1934.

25. Jackson, I. J.: Aseptic Meningitis Due to Blood and Its Breakdown Products: An Experimental and Clinical Study, Thesis, McGill University, no. 380006, 1947, p. 29.

26. Dandy, W. E.: The Brain, in Lewis, D.: The Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1948, vol. 12, chap. 1, p. 291.

27. Wycis, H. T.: Subdural Hygroma: A Report of Seven Cases, J. Neurosurg. **2**:340-357, 1945.

The large amounts of protein and fluids lost in the subdural space and their importance in the management of these infants are shown in the following 2 cases.

CASE 1.—An infant, 6 months of age (table 1), weighing 13 pounds (5,897 Gm.), received thirteen subdural aspirations. Quantity of fluid withdrawn each time ranged from 80 to 200 cc. The protein content of each specimen of fluid was from 376 to 1,480 mg. per hundred cubic centimeters. This patient lost approximately 1 Gm. of protein with each aspiration, which amounts to roughly .5 per cent of his daily protein needs. The actual fluid lost with each aspiration was 10 to 20 per cent of his daily requirements. Without the aid of intravenously administered glucose in isotonic sodium chloride solution and distilled water, plasma and blood this infant obviously would not have survived his procedures (subdural aspirations and craniotomy). He was unable to take the much needed extra fluids and proteins by mouth but could care for his normal requirements by

TABLE 1.—*Loss of Protein Through Subdural Aspirations in Infant (Case 1) Six Months of Age* *

Date	Amount of Subdural Fluid Aspirated, Cc.	Total Protein of Aspirated Fluid, Mg. per 100 Cc.	Actual Amount of Protein Lost Through Aspiration, Gm.
12/ 3	325	376	1.212
12/ 7	145	1,324	1,920
12/15	200	972	1.944
12/18	120	738	0.885
12/19	160	1,324	2.118
12/21	100	1,480	1.480
12/22	240	628	1.508
1/ 7	170	742	1,261
1/ 8	150	800	1.200

* This patient lost approximately 5 per cent of his daily protein requirements through the subdura aspirations.

oral feedings. At the time of his last aspiration, his blood proteins were reported to be 7.40 Gm. per hundred cubic centimeters.

CASE 2.—An infant who entered the hospital at the age of 3 months (table 2), weighing 9½ pounds (4,309 Gm.), underwent twenty-two subdural aspirations. The daily amount of fluid withdrawn ranged from 40 to 100 cc. and the quantity of protein with each aspiration was 580 to 2,940 mg. per hundred cubic centimeters. With each aspiration, this infant lost approximately 5 per cent of her daily protein requirments and 10 to 20 per cent of her daily fluid requirements. Following these punctures and two bilateral trepanations, the patient became edematous about the face and extremities and cyanotic (due to pulmonary edema). The red blood count, hemoglobin concentration and blood protein values were low. The edema was observed on the fifth day of continuous subdural drainage following the last trepanation. Glucose infusions were therefore discontinued, and immediate blood transfusions and plasma intravenously were administered. Under such therapy, the edema disappeared and a normal protein and fluid status was established.

In most instances, the quantity of fluid aspirated did not represent the entire amount of fluid present in the subdural space. If the entire

amount of fluid were aspirated from the subdural space, it would probably exceed the 10 to 20 per cent of the daily need. This slow but gradual loss of fluid and protein into the subdural space is one reason for the pale and undernourished-appearing infant.

The nutritional problem becomes most acute when the infant, in addition to losing protein and fluids in the subdural space, presents feeding difficulties. Many of these patients are able to take by mouth the normal diet for their age but are not able to take the large amounts of protein needed under these abnormal circumstances. The easiest,

TABLE 2.—*Loss of Protein Through Subdural Aspirations in Infant (Case 2) Three Months of Age* *

Date	Amount of Subdural Fluid Aspirated, Cc.	Total Protein of Aspirated Fluid, Mg. per 100 Cc.	Actual Amount of Protein Lost Through Aspiration, Gm.
11/30	50	.....	.....
12/ 1	50	.....	.....
12/ 3	80	2,940	2.35
12/ 5	150	1,380	2.07
12/18	100	.....	.....
12/22	150	.....	.....
12/28	90	.....	.....
1/ 2	45	1,140	0.513
1/ 9	90	1,140	1.026
1/13	65	960	0.627
1/15	68	790	0.530
1/17	95	1,020	0.969
1/19	105	580	0.609
1/20	40	1,740	0.696
1/21	65	980	0.637
1/23	70	800	0.560
1/25	62	920	0.560
1/26	20	1,140	0.228
1/27	60	1,280	0.768

* This patient lost approximately 5 per cent of her daily protein requirements through subdural aspiration. Shortly after the last aspiration, continuous drainage was instituted; the patient then became edematous. Intravenous administration of protein quickly restored her normal protein-fluid balance.

quickest and most efficient method of restoring the lost protein is by intravenous means. We have shown in 1 patient what can happen when only the fluid balance is cared for and the proteins neglected. Therefore, when caring for these chronically ill infants, blood plasma or commercially prepared protein solutions for intravenous use should be administered during the preoperative and postoperative periods. The small daily blood transfusions of 10 cc. per pound (0.5 Kg.) have been helpful in quickly restoring their nutritional balance. Frequent high caloric and high protein feedings by stomach tube are advantageous after the acute period has passed.

When the subdural hematomas and effusions are removed by means of craniotomy, blood should be given during the operation and in the

early postoperative period, even though the surgeon believes that there has been little loss of blood as a result of the procedure. The sudden removal of a large quantity of blood and fluid from the subdural space at the time of operation is often sufficient to cause shock.

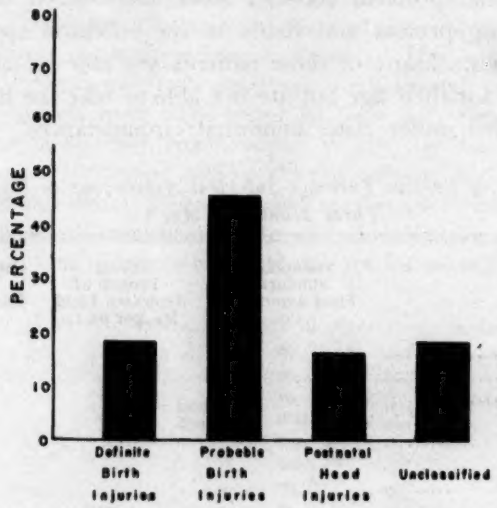

Fig. 7.—The incidence of the four etiologic groups among 55 cases of subdural effusions and hematoma.

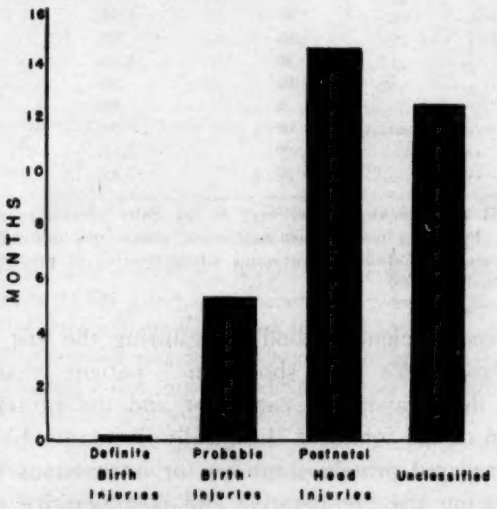

Fig. 8.—Average age on admission to the hospital of children in the four etiologic groups of subdural effusions and hematoma.

SUMMARY AND CONCLUSIONS

Fifty-five consecutive cases of subdural effusion and hematoma in infants are analyzed and subdivided into four groups, namely, definite birth injuries, postnatal head injuries and an unclassified group (fig. 7). The average age incidence is shown in figure 8. Cranial trauma, either

natal (36 cases) or postnatal (9 cases), was the greatest causative agent. The stress and strain on the fetal head during molding is the greatest factor in the production of trauma. Thus, what appears to be a normal labor and delivery may be sufficient to cause intracranial damage.

Fig. 9.—Symptomatology and physical findings in 55 cases of subdural effusion and hematoma. The columns above the names of the symptoms or findings represent total in each etiologic group, while the columns (solid black) below the title represent the total per finding among the 55 cases.

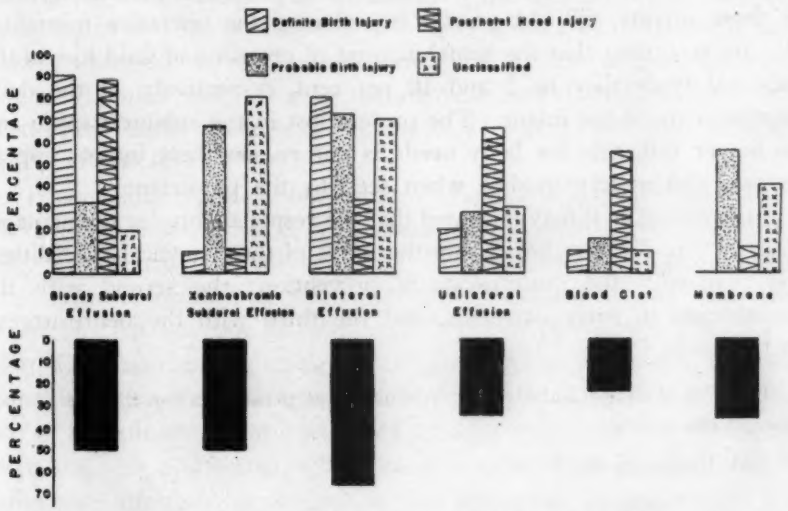

Fig. 10.—Pathologic changes in 55 cases of subdural effusions and hematoma. The columns above the names of the changes represent the total in each etiologic group, while the columns below (solid black) represent the total changes among 55 cases.

The symptomatology (fig. 9) and pathologic changes (fig. 10) offer striking characteristic features under each etiologic heading but vary when all cases are grouped together. Nevertheless, an infant with hydrocephalus, seizures or focal neurologic signs deserves consideration.

Subdural puncture is the only method of making an accurate diagnosis. Pneumography in early diagnosis offers the advantage of outlining the extent of the effusion and differentiating from other causes of hydrocephalus and seizures, while in the postoperative period it is helpful in determining whether the subdural space is obliterated.

The surgical treatment consists of emptying the subdural space and completely removing the membranes when they are present. The acute subdural hematoma, as in the group with definite birth injuries, is best treated by aspiration, for no membrane is usually present at this early stage. The chronic subdural effusion, as in the group of probable birth injuries and the unclassified group, is most satisfactorily treated, after confirmation of diagnosis by subdural tap, by trepanation for identification of membranes and, if their presence is confirmed, by early complete removal of the inner membrane. It is in these groups that membranes are commonly found. We believe that the complete removal of the inner membrane is most important, for it is this structure that prevents normal expansion of the brain. Since these membranes are apt to cover the whole hemisphere, a portion remaining over one pole will restrict its expansion and thereby increase the potentiality toward mental retardation.

Careful attention to the fluid and protein balance in the management of these infants will aid greatly in reducing the operative mortality. We are recording that the actual amount of protein and fluid lost in the subdural space may be 5 and 10 per cent, respectively, of the daily requirements of the infant. The protein lost in the subdural space and no longer utilizable for body needs is one reason these infants appear so pale and undernourished when seen by the physician.

In conclusion, it may be stated that the responsibility for the management of this disorder lies within the scope of three medical specialities: the first with the obstetrician in prevention; the second with the pediatrician in early diagnosis, and the third with the neurosurgeon in treatment.

Prof. W. Penfield and Dr. W. V. Cone gave permission for the use of their cases in this review.

3801 University Street (2).

MORPHOLOGIC CHARACTERISTICS AND ANTIBIOTIC RESISTANCE OF HEMOPHILUS INFLUENZAE

G. E. FOLEY
H. SHWACHMAN
M. McGARRY
AND
W. D. WINTER JR.
BOSTON

MENINGITIS due to Hemophilus influenzae is a relatively common disease. That it is a disease primarily of the young and that the mortality of untreated patients varies with the age of the patient are well recognized. For the past fifteen years H. influenzae has ranked first as a cause of bacterial meningitis at the Boston Children's Hospital. The only recent exceptions were the years 1943 and 1944, when there was a high incidence of meningococcic meningitis in the Boston area. Fothergill [1] summarized the data from the Children's Hospital from 1933 to 1936; of a total of 190 cases of bacterial meningitis, exclusive of tuberculous meningitis, 51, or 27 per cent, were due to H. influenzae. During the six year period, 1942 to 1947, of a total of 338 cases of bacterial meningitis, 115, or 34 per cent, were due to H. influenzae.

Inasmuch as relatively few data are available concerning the seasonal incidence of this disease, it is of interest to summarize this information (fig. 1). During the last six years, 1942 to 1947 inclusive, 115 children with H. influenzae meningitis were admitted to the Children's Hospital. All but one showed type B. The percentage incidence is plotted by months, beginning with August as the low point, on semilogarithmic paper. The upper curve represents the seasonal distribution of H. influenzae, untyped, based on 3,617 single cultures of material from the nose and throat, exclusive of cultures from persons with H. influenzae infections, examined in the laboratory during a two year period, July 1946 to July 1948. The total admissions to the hospital

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From the Division of Laboratories and Research, The Children's Medical Center, and the Department of Pediatrics, Harvard Medical School.

Presented before the Laboratory Section of the American Public Health Association at the Seventy-Sixth Annual Meeting, Boston, Nov. 10, 1948.

1. Fothergill, L. D.: Hemophilus Influenzae (Pfeiffer Bacillus) Meningitis and Its Specific Treatment, New England J. Med. **216**:587-590, 1937.

during the same period were 15,451. Although the curve represents the results of cultures taken on only 23.4 per cent of the total patients admitted to the hospital, there appears to be a simultaneous seasonal variation in the recovery of H. influenzae from the nose and throat and in the occurrence of H. influenzae meningitis. The order and amplitude of this seasonal fluctuation are similar to those observed to be characteristic of other diseases of the upper respiratory tract of bacterial origin.[2]

The sharp decrease in the mortality of H. influenzae meningitis during the past decade can be attributed to the introduction of the following agents, used singly or in combination: Alexander's rabbit serum, sulfadiazine and antibiotic substances.[3] The effect of two of these substances, not necessarily of equal therapeutic value, on the H. influenzae isolated from patients with meningitis is the subject of this report.

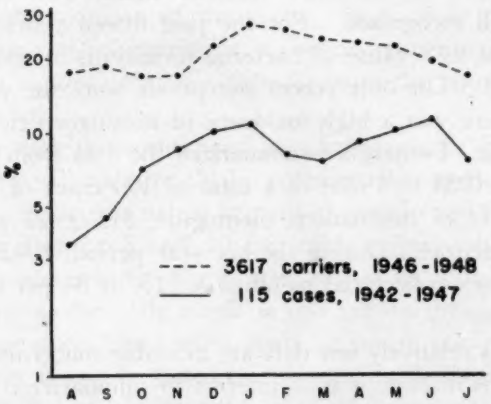

Fig. 1.—Graph showing seasonal variation of H. influenzae in cultures of material from the nose and throat (broken line) in 3,617 carriers from 1946 to 1948, and of H. influenzae, type B, meningitis (solid line) in 115 patients admitted to the hospital from 1942 to 1947.

IN VITRO SENSITIVITY TO PENICILLIN AND STREPTOMYCIN

In the past eighteen months, the in vitro sensitivity to penicillin G and streptomycin sulfate has been determined for the strains of H. influenzae, type B, isolated from the spinal fluids of 41 persons with meningitis. During this same period, similar observations have been

2. Aycock, W. L.; Foley, G. E., and Hendry, K. H.: The Epidemiologic Significance of Amplitudes of Seasonal Fluctuation in Infectious Diseases, Am. J. M. Sc. **211**:709-717, 1946.

3. Alexander, H. E.; Ellis, C., and Leidy, G.: Treatment of Type-Specific Hemophilus Influenzae Infections in Infancy and Childhood, J. Pediat. **20**:673-698, 1942. Alexander, H. E.: Streptomycin in Pediatrics, ibid. **29**:192-198, 1946.

made on 24 non-type-B strains of H. influenzae isolated from the nose or throat cultures of other hospitalized patients. After isolation, all strains were maintained in the frozen state until the tests for sensitivity were done.

Sensitivity in vitro was determined by a procedure based on the methods described by Price, Nielsen and Welch [4] and Randall, Price and Welch [5] for the assay of antibiotic levels in body fluids. The antibiotic material was diluted so that four times the desired final concentration was contained in a volume of 0.5 cc. of medium and diluted serially by 50 per cent increments. To each tube was added 1.5 cc. of a 1:100 dilution of an eighteen-hour culture. The preparations

TABLE 1.—*In Vitro Sensitivity to Penicillin and Streptomycin on Original Isolates of H. Influenzae from Patients and Carriers (Titration Method)*

	Penicillin G					Streptomycin Sulfate			
	Meningitis Strains		Nose and Throat Strains			Meningitis Strains		Nose and Throat Strains	
Oxford Units/Cc.	No.	%	No.	%	Mg./Cc.	No.	%	No.	%
20.0-20.0+	14	35.0	10	41.2					
10.0	5	12.5	1	4.2					
5.0	3	7.5	1	4.2					
2.5	1	2.5	2	8.4					
1.25	4	10.0	..	....					
0.62	1	2.5	5	21.0					
0.31	6	15.0	4	16.8	0.032	1	2.4	1	4.2
0.15	4	10.0	1	4.2	0.016	3	7.2	1	4.2
0.07	1	2.5	..	....	0.008	5	12.0	2	8.4
0.04	1	2.5	..	....	0.004*	13	32.0	3	12.4
					0.002	18	44.0	4	16.8
					0.001	1	2.4	13	54.0
Total	40†		24			41		24	

* The minimal inhibiting dose of 1 strain was increased to 2 mg. per cubic centimeter and that of another to 64 mg. per cubic centimeter during therapy.
† One strain was not tested.

were incubated at 37 C. (98.6 F.) for eighteen to twenty-four hours. The first tube in which no growth occurred was taken as the minimal inhibiting dose (M. I. D.). Strains of Bacillus subtilis and Bacillus circulans obtained from the Food and Drug Administration were used as controls on the penicillin and the streptomycin, respectively. The medium used was the semisynthetic liver infusion broth described by Dingle and Fothergill.[6] Parallel titrations on the same strains in this

4. Price, C. W.; Nielsen, J. K., and Welch, H.: Estimation of Streptomycin in Body Fluids, Science **103**:56-57, 1946.

5. Randall, W. A.; Price, C. W., and Welch, H.: Estimation of Penicillin in Body Fluids, Science **101**:365-366, 1945.

6. Dingle, J. H., and Fothergill, L. D.: The Isolation and Properties of the Specific Polysaccharide of Type B Hemophilus Influenzae, J. Immunol. **37**:53-63, 1939.

and in Fildes' medium [7] showed no significant differences in the end points. The growth of the majority of strains of H. influenzae in the Dingle-Fothergill medium was ample. Since this medium is clear and contains a small amount of phenolsulfonphthalein, the end points were easily read. Its use for measurements of sensitivity is recommended.

As may be seen from table 1, there was little difference between the strains of H. influenzae, type B, from the spinal fluid and the non-type-B strains as regards sensitivity to penicillin or streptomycin. The majority of strains in both groups required 2.5 or more Oxford units of penicillin for complete inhibition, whereas the majority of strains in both groups were inhibited by 0.004 mg. or less of streptomycin. It should be noted that of the 41 strains from spinal fluid, only 2 showed any significant increase in resistance to streptomycin during therapy.

COMPARISON OF TUBE AND CUP METHODS FOR DETERMINATION OF ANTIBIOTIC SENSITIVITY

The antibiotic sensitivities of 22 strains of H. influenzae, type B, from spinal fluid were determined by the usual cup method on 5 per cent horse blood agar plates streaked heavily with micro-organisms from a chocolate agar slant or Dingle-Fothergill broth culture which had been incubated eighteen hours at 37 C. The lowest concentration giving a zone of inhibition greater than 1 to 2 mm. in diameter was taken as the minimal inhibiting dose.

Comparison of these data with those obtained by the serial tube titration method applied to the same strains revealed a surprising lack of correlation (fig. *2A*). With consideration of one dilution of a 50 per cent increment as insignificant in either the titration or the cup technic, in no instance was the minimal inhibiting dose of penicillin identical by both methods. Four strains, or 18 per cent (dots, fig. *2A*), required a higher concentration of penicillin for inhibition in the cup method, while the remaining 18 strains (82 per cent) were inhibited in the cup method by from one third to one two thousandth (average, one-five hundredth) of the minimal inhibiting dose as determined by serial titration. This lack of correlation is further emphasized by the observation (fig. *2A*) that of 3 strains inhibited by 0.32 Oxford unit of penicillin per cubic centimeter by serial dilution, the minimal inhibiting doses by the cup method were 0.01, 1.0 and 10.0 Oxford units, respectively.

The same general lack of correlation between the two methods, but perhaps to a somewhat lesser extent, was observed with streptomycin (fig. *2B*). The same minimal inhibiting dose was obtained

7. Fildes, P.: A New Medium for the Growth of B. Influenzae, Brit. J. Exper. Path. **1**:129-130, 1920.

with 7 strains, or 32 per cent (circles, fig. 2 *B*), by either method, while 1 strain, or 5 per cent (square, fig. 2 *B*), gave a higher minimal inhibiting dose by the cup than by the tube titration method. The remaining 14 strains (63 per cent) were inhibited in the cup method by one half to one fortieth (average, one seventh) of the minimal inhibiting dose as determined by serial tube titration.

MORPHOLOGIC ASPECTS OF H. INFLUENZAE

The morphologic characteristics of 24 strains of H. influenzae, type B, from spinal fluid were studied and 22 (92 per cent) were observed to be definitely pleomorphic and produced the so-called large bodies and pleuropneumonia-like variants described by Dienes in this and other species [8] when examined immediately on primary isolation by proper *in situ* colony-staining technics [9] (fig. 3, *1* and *2*). Similar

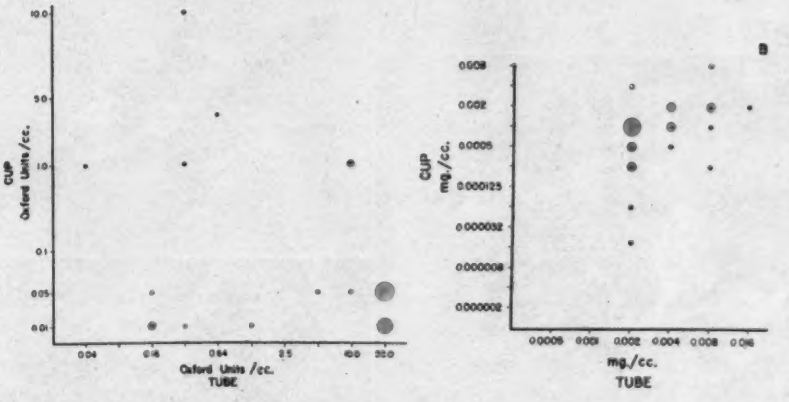

Fig. 2.—Graphs showing sensitivity of H. influenzae, type B, by the tube and cup methods. *A* shows sensitivity to penicillin. The dots represent strains with higher minimal inhibiting dose in cup than in tube titration. The circles represent strains with higher minimal inhibiting dose in tube than in cup titration. The concentric circles represent numbers of observations falling on same point. *B* shows sensitivity to streptomycin. The dots represent strains with higher minimal inhibiting dose in tube than in cup titration. The circles represent strains with same minimal inhibiting dose in either titration. The squares represent strains with higher minimal inhibiting dose in cup than in tube titration. Concentric circles represent numbers of observations falling on same point.

but less pronounced "pleomorphism" was observed also in some respiratory strains when examined by the same technics. These char-

8. Dienes, L.: L Type Variant Forms in Cultures of Various Bacteria, Proc. Soc. Exper. Biol. & Med. **42**:636-640, 1939; L Type of Growth in Cultures of a Hemolytic Parainfluenza Bacillus, ibid. **55**:142-144, 1944; A Peculiar Reproductive Process in Colon Bacillus Colonies, ibid. **42**:773-778, 1939; Origin of L Type Colonies in Bacterial Cultures, ibid. **43**:703-704, 1940.

9. Dienes, L., and Smith, W. E.: The Significance of Pleomorphism in Bacteroides Strain, J. Bact. **48**:125-153, 1944.

acteristics disappeared after short periods of cultivation on artificial mediums, the morphologic characteristics of the strain then becoming those of the simple bacillary form usually associated with H. influenzae.

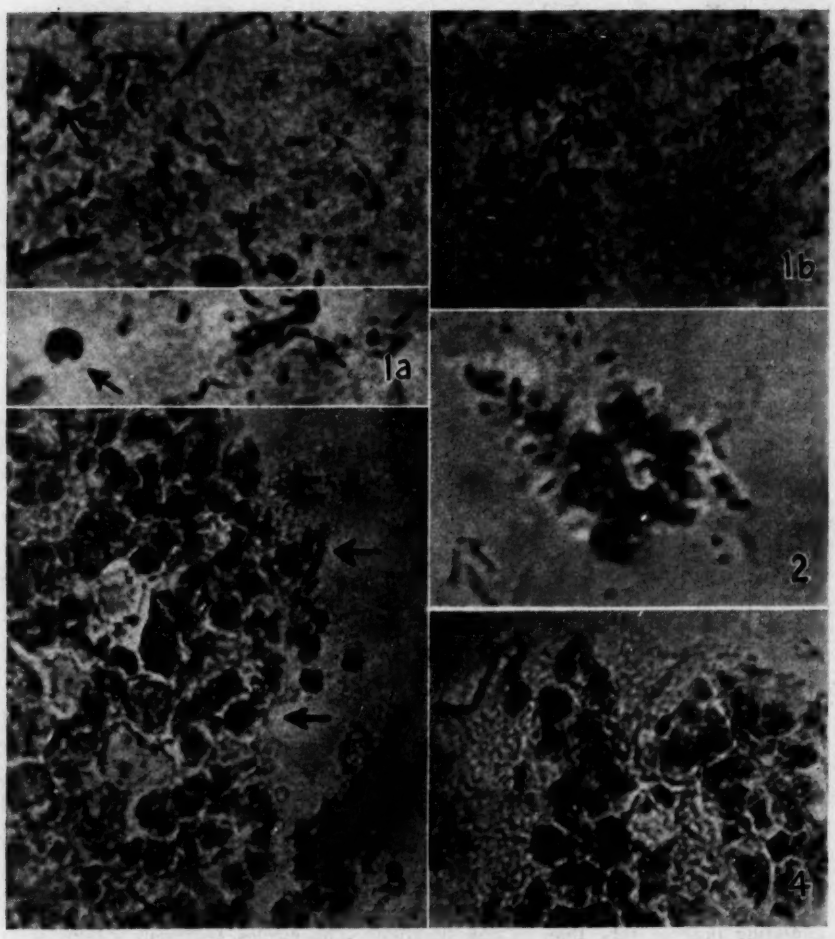

Fig. 3.—*1a,* impression preparation from a four hour plate culture of H. influenzae, type B, second generation from spinal fluid, with no exposure to antibiotic material; methylene blue stain, × 1,400. *1b,* same preparation as *1a,* but from a different strain. Note "large bodies" and filamentous cells.

2, pleuropneumonia-like variant of H. influenzae, type B, second generation from spinal fluid, with no exposure to antibiotic substances. It is an agar block preparation from a seven hour plate culture; methylene blue stain, × 1,100. Note "large bodies," tiny coccobacillary cells and depth of colony in agar. The greater portion of the colony is beneath the surface of the agar, out of focus.

3 and *4,* agar block preparation from a twenty-four hour culture on a plate containing 0.25 Oxford unit of penicillin per cubic centimeter; methylene blue stain, × 3,000. Colonies are composed almost entirely of "large bodies," some of which are vacuolated and some of which show varying degrees of fragmentation. Note filamentous cells at periphery of colony.

Brief exposure to streptomycin or penicillin induced morphologic changes in these strains comparable to those described by Dienes.[10] The bacillary cells became swollen; some appeared to undergo a process of fragmentation, and an occasional pleuropneumonia-like variant could be seen on agar blocks. The latter, either naturally occurring or induced, could not be isolated in pure culture.

Agar block preparations made from the cup sensitivity plates frequently revealed, as pointed out by Dienes,[10] that in the zone of apparently complete inhibition around the cup there were many submacroscopic or, even, microscopic colonies composed of large, swollen, fragmenting cells, as well as an occasional pleuropneumonia-like variant (fig. 3, *3* and *4*). Agar blocks containing such colonies yielded pure cultures of typical H. influenzae when smeared *in toto* over the surface of a 5 per cent horse blood agar plate which was then incubated at 28 or 37 C. (82.4 or 98.6 F.) for eighteen to twenty-four hours. This type of colony appeared in the zones of inhibition produced by two to one hundred times the minimal inhibiting dose of penicillin, as well as in those produced by two to ten times the minimal inhibiting dose of streptomycin, suggesting that, in this form, the cell exhibits increased resistance to these antibiotic substances. A similar increase in antibiotic resistance was observed by Stubblefield [11] in a round cell variant of Colobactrum coli. However, in the case of H. influenzae, daughter cultures of these round cell variants showed no significant increase in resistance to streptomycin.

On the other hand, the same phenomena appeared when the strain was exposed to a fraction of the minimal inhibiting dose. These observations suggested that the appearance of morphologic cycles may represent something more fundamental than a response to injury [12]; in this instance, the basis perhaps may be the development of a means of survival following exposure to an injurious environment, since Dienes [13] and Shanahan and his associates [14] observed that morphologic variants induced by simple toxicity do not reproduce.

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10. Dienes, L.: Isolation of Pleuropneumonia-Like Organisms from Cultures of H. Influenzae, J. Bact. **54**:3, 1947.

11. Stubblefield, E.: A Morphological Varient of E. Coli and Its Resistance to Streptomycin, J. Bact. **54**:569-573, 1947.

12. Scales, F. M.: Induced Morphological Variation in B. Coli, J. Infect. Dis. **29**:591-610, 1921.

13. Dienes, L.: Reproductive Processes in Proteus Cultures, Proc. Soc. Exper. Biol. & Med. **63**:265-270, 1946.

14. Shanahan, A. J.; Eisenstark, A., and Tanner, F. W.: Morphology of E. Coli Exposed to Penicillin as Observed with the Electron Microscope, J. Bact. **54**:183-189, 1947.

IN VIVO STUDIES

In agreement with the experience of others,[15] the erratic behavior of mucin suspensions of H. influenzae, type B, in mice complicated

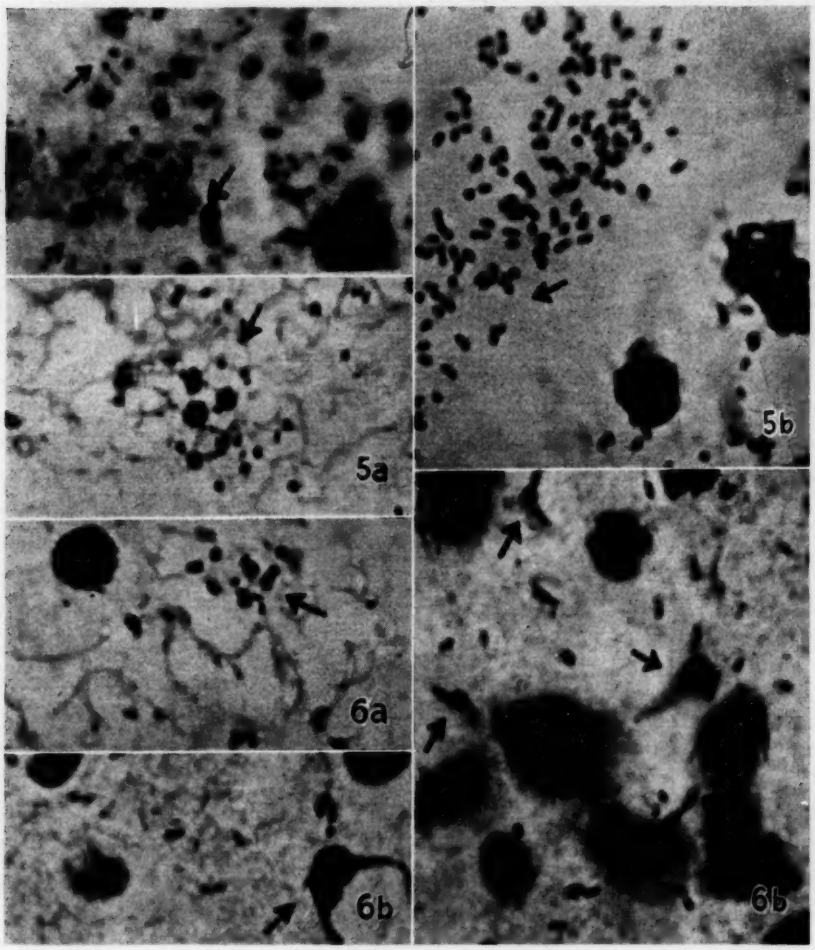

Fig. 4.—*5a,* forty-eight hour culture in a 9 day chick embryo; Gram stain, × 1,400. There was no exposure to an antibiotic substance. Note "large bodies" and usual coccobacillary cells. Photomicrograph also contains two chicken blood cells. *b,* twenty-four hour culture in a 12 day chick embryo; Gram stain, × 1,400. Culture not exposed to antibiotic material. Note the usual coccobacillary morphologic aspect. Photomicrograph also contains chicken blood cells.

6a, forty-eight hour culture in a 12 day chick embryo containing 0.025 Oxford unit of penicillin; methylene blue stain, × 1,400. Note small coccobacillary cells and numerous "large bodies." *b,* twenty-four hour culture in a 9 day chick embryo containing 200 Oxford units of penicillin; methylene blue stain, × 1,400. Note long, angulated, filamentous cells attached to "large bodies."

15. Gordon, M., and Zinnemann, K.: The In-Vitro Sensitivity of H. Influenzae to Penicillin, with Special Reference to Meningeal Strains of Pittman's Type B, Brit. M. J. **2**:795-796, 1945.

all attempts to obtain in vivo sensitivity titrations. Since the chorioallantoic membrane of the chick embryo has been used for the cultivation of H. influenzae,[16] as well as for the determination of the antibiotic sensitivity of a number of micro-organisms,[17] in vivo studies in the chick embryo were undertaken.

Fertile eggs were incubated at 37.5 to 38.5 C. (99.5 to 101.3 F.) and turned daily for eight to eleven days. The eggs were then candled for viability, the position of the air sac noted and the chorioallantoic membrane exposed and inoculated by the usual window technic.

Preliminary experiments indicated that the average minimal infecting dose of H. influenzae for the chorioallantoic membrane was about 12 to 1,400 bacilli. The strains used in antibiotic titrations were incubated overnight on chocolate agar slants, and one loopful of the resulting growth was suspended in 2.5 cc. of isotonic sodium chloride solution (approximately a 1 : 250 dilution). Each chick embryo was inoculated on the chorioallantoic membrane with 0.05 cc. of such a suspension, this volume representing several minimal infecting doses.

Penicillin G and streptomycin sulfate were diluted with saline solution in such a way that the desired dose was contained in 1 cc. placed on the chorioallantoic membrane. The doses titrated in eggs represented multiples of 10 or fractions by 10 of the minimal inhibiting dose as determined by tube titration. The infecting dose was inoculated six hours after the antibiotic material and the eggs incubated at 37 C. Presence or absence of growth was determined by daily smears of the chorioallantoic membrane until the embryo died, or for a period of three days.

Since the true end point was difficult to interpret because of the varying susceptibility of H. influenzae to the same dose of antibiotic material in different eggs, the 50 per cent inhibiting dose was computed from the observed data according to the method of Reed and Muench.[18] The results of five such titrations, based on observations made on 225 chick embryos, are compared with the corresponding in vitro 50 per cent end points in table 2.

The strains of H. influenzae listed in table 2 were selected for in vivo study because of their relative resistance (strains 1, 2 and 3) or susceptibility (strains 4 and 5) to penicillin. It may be seen that

16. Gallavan, M.: Encephalitis and Meningitis in Chick Embryo Following Inoculation of Chorioallantoic Membrane with H. Influenzae, Am. J. Path. **13**:911-926, 1937.

17. Kempe, C. H.; Shaw, E. B., and Silver, H. K.: Clinical Applications of Chick Embryo Cultures: I. Primary Diagnosis of Meningitis and Study of Spinal Fluid in Meningococcemia Without Meningitis; II. In Vivo Streptomycin Sensitivity Test, Am. J. Dis. Child. **72**:281-288 (Sept.) 1946.

18. Reed, L. J., and Muench, H.: A Simple Method of Estimating Fifty Per Cent Endpoints, Am. J. Hyg. **27**:493-497, 1938.

there is poor correlation between the in vitro and in vivo minimal inhibiting doses. The two strains which appeared to be relatively sensitive (strains 4 and 5) required 2 to 3 times the in vitro concentrations for inhibition in vivo. The results with streptomycin also were divergent, a strain relatively resistant (strain 2) in vitro being the most sensitive in vivo. It should be noted that the minimal inhibiting dose in vivo of streptomycin was uniformly less than the minimal inhibiting dose in vitro.

MORPHOLOGIC MODIFICATIONS IN EGGS

The morphologic modifications of H. influenzae on the chorioallantoic membrane are worthy of mention. Certain strains became pleomorphic and produced the so-called large bodies in untreated eggs, while the presence of penicillin or, to a lesser extent, streptomycin on the chorioallantoic membrane induced these morphologic changes in all the strains so tested (fig. 4, *5* and *6*).

TABLE 2.—*Comparison of Sensitivity of H. Influenzae Type B, in Vitro and in Vivo, to Penicillin and Streptomycin (50 Per Cent of Minimal Inhibiting Dose)*

Strain	Penicillin G, Oxford Units/Cc.		Streptomycin Sulfate, Micrograms/Cc.	
	Egg*	Tube	Egg*	Tube
1	1.0	14.0	0.2	2.8
2	0.8	4.0+	0.09	11.0
3	0.15	4.0+	0.4	11.0
4	0.5†	0.18	0.7	11.0
5	0.45†	0.23	0.15	1.4

* Dose per cubic centimeter computed on basis of 50 cc. as average volume of egg.
† More resistant in vivo.

COMMENT

The strains of H. influenzae, type B, isolated from the spinal fluids of 41 patients with meningitis were all sensitive to small doses of streptomycin. A few of the strains included in this series were somewhat more resistant than those reported by Alexander and Leidy.[19]

The uniformly greater sensitivity to streptomycin in the chick embryo as contrasted to that in test tube titrations is in accord with similar observations made by Kempe and his co-workers [17] with other micro-organisms. However, Alexander and Leidy [19] observed the mouse protective dose to be much higher than would be expected judging from the inhibiting dose in vitro.

There are numerous references in the literature stating that H. influenzae is resistant to penicillin.[20] Bloomfield, Armstrong and

19. Alexander, H. E., and Leidy, G.: Influence of Streptomycin on Type B H. Influenzae, Science **104**:101-102, 1946.

20. Keefer, C. S.; Herwick, R. P.; Van Winkle, W., Jr., and Putnam, L. E.: New Dosage Forms of Penicillin: Statement Concerning Certifiable Penicillin Products Including Recommended Indications, Dosage and Precautions, J. A. M. A. **128**:1161-1164 (Aug. 18) 1945.

Kirby [21] reported a case of H. influenzae infection which did not respond to penicillin. On the other hand, Gordon and Zinnemann,[15] Forgacs, Hutchinson and Rewell [22] and North, Wilson and Anderson [23] reported several strains of H. influenzae to be quite sensitive to penicillin in vitro. The last-named authors reported the successful penicillin therapy of infection with H. influenzae in mice, while McIntosh and Drysdale [24] reported a case of H. influenzae meningitis which responded to penicillin and sulfonamide therapy.

The results of the present study confirm the observations of others[25] that some strains of H. influenzae are sensitive to penicillin, although the majority of strains tested required more than 2.5 Oxford units per cubic centimeter for inhibition. There was no consistent relationship, however, between the in vivo and the in vitro concentrations required for inhibition, although all the strains so tested were inhibited by relatively low doses in the chick embryo.

The morphologic aspects of H. influenzae freshly isolated from spinal fluid present decided variation from those of a laboratory strain. When appropriate technics are employed, the morphologic cycles similar to those which have been observed with other micro-organisms are easily demonstrated. This morphologic variation is lost by cultivation on artificial mediums, but can be induced in some strains by cultivation in chick embryo or in nearly all strains by exposure to penicillin or streptomycin on an agar plate. The significance of these morphologic changes is not fully understood. The disappearance of these variants in subculture differentiates them from those described by Shibley and Hoelscher [26] in the R colonies of Hemophilus pertussis. The present experiments suggest that the appearance of morphologic variants may represent something more fundamental than a toxic response. Their spontaneous appearance on artificial mediums in freshly isolated strains, their appearance in chick embryo in an otherwise non-

21. Bloomfield, A. L.; Armstrong, C. D., and Kirby, W. M. M.: Treatment of Subacute Bacterial Endocarditis with Penicillin, J. Clin. Investigation **24**:251-257, 1945.

22. Forgacs, P.; Hutchinson, R. J., and Rewell, R. E.: Penicillin Sensitivity of H. Influenzae: Two Sensitive Pathogenic Strains, Lancet **1**:785-786, 1945.

23. North, E. A.; Wilson, H., and Anderson, G.: The Resistance of H. Influenzae to Penicillin, with Special Reference to Type B Strains, M. J. Australia **1**:626-629, 1946.

24. McIntosh, D. G., and Drysdale, C. F.: Meningitis Due to Penicillin and Sulfonamide-Sensitive Pittman Type B Strains of H. Influenzae with Recovery, Brit. M. J. **2**:796-797, 1945.

25. Forgacs and others.[22] North and others.[23]

26. Shibley, C. S., and Hoelscher, H.: Studies on Whooping Cough: I. Type-Specific (S) and Dissociation (R) Forms of Hemophilus Pertussis, J. Exper. Med. **60**:403-418, 1934.

pleomorphic strain and their appearance following exposure to sulfonamide drugs and a variety of toxic salts, as well as to minimal and maximal concentrations of antibiotic substances, all suggest that these changes may represent a means of survival and adaptation to an ordinarily detrimental environment.

SUMMARY

H. influenzae meningitis is the commonest variety of bacterial meningitis encountered at the Boston Children's Hospital. The seasonal variation appears to be similar to the seasonal incidence of H. influenzae in the nose and throat. The order and amplitude of this variation are similar to those of other diseases of the upper respiratory tract of bacterial origin.

Sensitivities to penicillin and streptomycin as determined by test tube titration in a semisynthetic medium on 41 strains of H. influenzae, type B, isolated from spinal fluid and on 24 respiratory strains of H. influenzae indicated that all strains were inhibited by 0.001 to 0.032 mg. of streptomycin per cubic centimeter. The majority of strains were inhibited by 0.004 mg. or less of streptomycin per cubic centimeter. Sensitivity to penicillin showed greater variation, ranging from 0.04 to more than 20.0 Oxford units per cubic centimeter. The majority of strains required 2.5 or more Oxford units of penicillin per cubic centimeter. There was no significant difference in antibiotic sensitivity between the spinal fluid and respiratory strains.

A comparison of the antibiotic sensitivities of 22 strains of H. influenzae, type B, from spinal fluid indicated that there was little correlation in results obtained between the cup and tube titration technics used in this study.

A comparison of the sensitivities in vivo in chick embryo and in vitro by tube titration of 5 strains of H. influenzae, type B, from spinal fluid indicated that the in vivo inhibiting dose of streptomycin was consistently less than the in vitro values. The in vivo inhibiting doses of penicillin, on the other hand, were inconsistent; those for 3 strains were less than and those for 2 strains were greater than the corresponding in vitro inhibiting doses.

The morphologic variations observed in freshly isolated strains of H. influenzae, and in strains growing on the chorioallantoic membrane of the chick embryo or on agar containing antibiotic material are discussed.

As is well illustrated by the present study, the antibiotic sensitivity of a given strain varies with the technic used for its determination. Such values are significant only as a basis for comparison with other strains tested by the same technic in the same laboratory and are not necessarily an indication of the clinical response to be expected.

300 Longwood Avenue (15).

EXTERNAL ANORECTAL PROLAPSE IN CHILDREN DURING THE WAR YEARS

B. M. TORDOIR, M.D.
Surgeon, St. Canisius Hospital
NIJMEGEN, NETHERLANDS

IN NORMAL circumstances only occasional cases of external anorectal prolapse in children are seen, but during the war years there was a sharp increase in their number. The same observation was made in other countries.[1]

CAUSES

The anatomic predisposition of children for this disease is well known. The straight sacrum with the absence of a concave protecting excavatio rectococcygealis, the looseness and weakness of the connective tissues and sphincter and levator ani muscles around the rectum, the high position of the pelvic organs such as the bladder and uterus, with a deeply situated Douglas pouch, and the great mobility of the mesocolon, all play their parts. In several published reports of series of cases the majority was made up by girls and explained mainly on the basis of the aforementioned anatomic facts. In my series the majority was, however, formed by boys.

Jeanel and Verneuil [2] emphasized the importance of the pelvic musculature, which, if normal, should prevent the development of a prolapse even when the sphincter muscle has been previously cut. Nevertheless, in normal circumstances the number of cases is limited. During the war years, however, the rations were gradually diminished both qualitatively and quantitatively to reach, finally, a near-starvation level. In particular, the economically poor classes of the population with their often large families suffered most, as they were unable to increase their rations by other means. The feces often became semiliquid and the condition necessitated prolonged and frequent use of the toilet. The straining and increased abdominal pressure were mainly responsible for the many prolapses. Since during those years nearly all young children had whooping cough, the factor of strain became even more highly important. Hygienic conditions became worse and resulted in

1. Krönke, E.: Der Darmvorfall des Kindes, Zentralbl. f. Chir. 8:840, 1947.
2. Jeanel and Verneuil, cited by R. Reichle, in Kirschner, M., and Nordmann, J.: Die Chirurgie, Berlin, Urban & Schwarzenberg, 1927, vol. 6, p. 707.

a high frequency of ascariasis, other infectious diseases besides the already mentioned whooping cough, and inflammatory processes of the intestinal tract with subsequent wasting of fat deposits like the ischiorectal fat mass which normally plays a large part in the fixation of the rectum. In some cases the diarrhea was purely of starvation origin and probably due to a lack of vitamins. Of influence also may have been a disturbance of the nervous apparatus of the anus, caused by altered alimentary factors.

METHODS OF TREATMENT

As a radical change in diet had to wait for peacetime conditions, all exciting factors, such as infectious diseases, diarrhea and ascariasis, were combated as far as possible.

The parents were told to improve the stool habits of their children, which meant they should prevent any prolonged use of the toilet and have the children defecate in a recumbent position. All patients had

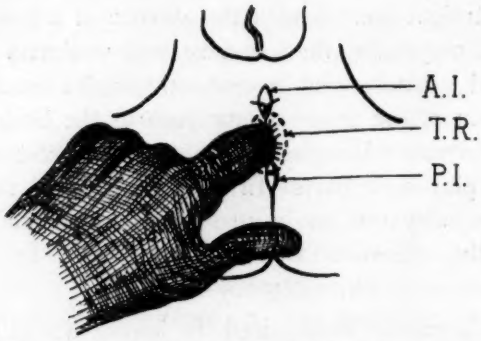

Fig. 1.—Drawing of anal region showing incisions for use of Thiersch ring in anorectal prolapse. *A.I.* indicates anterior incision, *T.R.*, the ring, and *P.I.* the posterior incision.

been treated previously by the family physician with conservative means, but the unsuccessfully treated patients were at a later date referred to this hospital. During the first years they were mainly hospitalized and operated on. In the operation, the wire ring method of Thiersch was used (fig. 1). I quote Kirschner[3] concerning this method:

> With the patient in the lithotomy position, two short radiating incisions are made, one in the anterior raphe, the other in the posterior raphe, about 2 cm. from the anal opening. A large curved needle provided with a fairly strong rustless steel wire is introduced through the anterior incision, and is carried around the anus and brought out through the posterior incision. The surgeon's left index finger introduced into the anus guards against injury to the mucosa. In a similar manner the needle is carried on the other side from the posterior

3. Kirschner, M.: Operative Surgery: The Abdomen and Rectum, translated by I. S. Ravdin, Philadelphia, J. B. Lippincott Company, 1933, vol 2, p 363.

to the anterior incision. The two ends of the wire protruding from the anterior incision are now twisted together until in adults the first phalanx of the surgeon's index finger, and in children only the tip, can just pass through the ring. The remaining ends of the wire are cut off, the twisted ends are bent inwards and the two skin incisions are sutured over the buried wire ring and sealed with collodion.

On account of the lack of metal wire I used silk. The wire, which is situated between the sphincter muscle and the skin, narrowed the opening of the anus considerably and supported it. But far more important, in my opinion, was the fibrous ring which developed afterward. In particular, this ring was formed in the many patients in whom inflammation followed the introduction of the ring of Thiersch. Several times the wire had to be removed because of the infection resulting at a later date.

Several circumstances forced me to use oftener the injection treatment (fig. 2) with quinine and urea hydrochloride.[4] Shortage of hospital beds caused by the many war casualties and financial factors often made hospitalization for the Thiersch operation impossible. Instead, injection treatment which could be given while the patient remained ambulatory was used. Moreover, for theoretic reasons we preferred the development of a fixation of the rectum by fibrous tissue above the sphincter muscle instead of below as with the ring of Thiersch.

Gaume [5] in 1939 was one of the first to treat rectal prolapse with injections of quinine and urea hydrochloride. Many authors [6] confirmed his good results obtained in children.

4. This preparation, a 3 per cent solution, known also as carbamidated quinine dihydrochloride, was put up by the pharmacy of this hospital in 5 cc. ampuls, according to the following prescription:

℞

Quinine hydrochloride	2.290 Gm.
Urea (pure)	0.370 Gm.
Hydrochloric acid, tenth normal	54 cc.

To make 100 cc.

5. Gaume, J. M.: Procidentia Recti, M. Rec. **149**:273, 1939.

6. Terrell, E. H., in discussion on Corbett, J. J.: Prolapse of Rectum in Children, Tr. Am. Proct. Soc. **29**:126, 1929. Welcker, A.: Practische kleine Chirurgie, Amsterdam, Netherlands, Van Holkema En Warendorf N.V., 1940, p. 381. Veen, J., and Hazenberg, A.: Injection Treatment of the Ano Rectal Prolapse in Children, Nederl. tijdschr. v. geneesk. **87**:1734, 1943. Kaplan, U.: Rectum Prolapse Treatment in Children with Sclerosing Injections of Quinine and Urea Hydrochloride, Cong. internal de med. trop. et d'hyg., Compt. rend. (1928) **3**:219, 1931. Bacon, H. E.: Anus, Rectum, Sigmoid Colon: Diagnosis and Treatment, ed. 2, Philadelphia, J. B. Lippincott Company, 1941, p. 414.

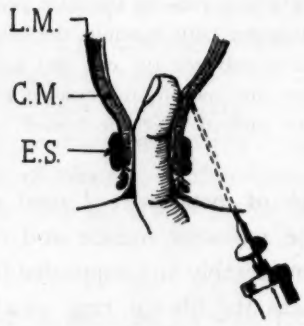

Fig. 2.—Cross section of anal region showing injection method of treatment in anorectal prolapse. *L.M.* indicates longitudinal muscle coat, *C.M.*, the circular muscle coat, and *E.S.*, the external sphincter muscle.

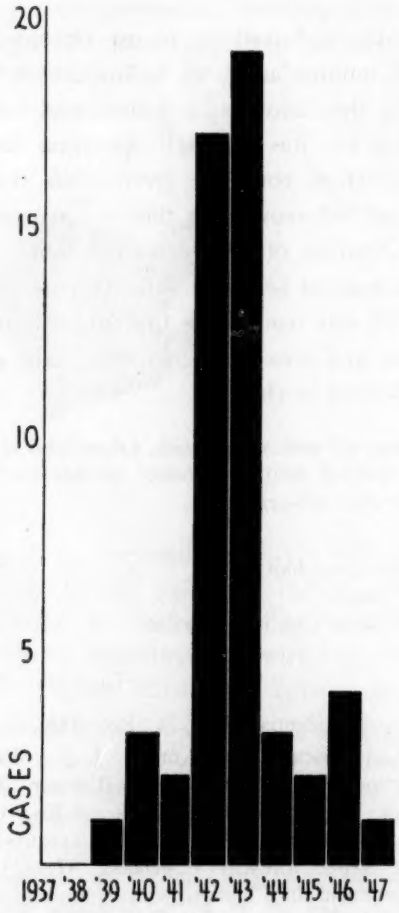

Fig. 3.—Graph showing number of cases of anorectal prolapse treated in St. Canisius Hospital, Nijmegen, Netherlands, during the years 1937 to 1947.

In the present cases I used the following technic: The patient was placed in the dorsal lithotomy position and the prolapse was—if necessary—reduced. With the surgeon's left index finger inside the lumen of the rectum four injections—one in each quadrant—of quinine and urea hydrochloride (4 × 1.25 cc.) were given. The needle was inserted through the skin approximately 2.5 cm. lateral to the anal margin. Guided by the surgeon's finger inside, the needle was driven upward until its point was felt. Beneath the mucosa a depot was injected. Injection into the sphincter muscle had to be avoided. In this way an excellent fixation of the rectum in the hollow of the sacrum was obtained by the resulting plastic periproctitis. For a few children it was necessary to repeat the injection.

Figure 3 shows clearly the high incidence during the hardest war years. The sharp drop in 1944 was caused mainly by actual warfare in this region during which war surgery had an over-all priority. Moreover, in this year the enemy occupation ended and rations gradually improved.

RESULTS OF TREATMENT

In particular I was interested in whether any degree of stricture caused by the fibrous ring had developed in the patients treated by the Thiersch method. The average age for the whole series was 2½ years. Procidentia—the prolapse of all layers of the rectal wall, characterized by protrusion of its circular muscle layer (compared with the protrusion of only the longitudinal layer in anorectal prolapse)—was never seen. The average length of the prolapse was 1 inch (2.5 cm.).

Of a total of 52 patients, 41 were admitted to the hospital for treatment with the ring method of Thiersch. The average stay in the hospital was nineteen days. In 7 patients inflammation developed, and the ring had to be removed. In several other children, after they had left the hospital the ring was expelled spontaneously or was removed because of suppuration. Exact data could not be obtained from the parents. There have been no recurrences.

Recent reexamination (January 1949) revealed that in all but 3 children the ring had given way. In none of them could a fibrous ring be felt. In 3 patients the ring was still intact and had caused considerable narrowing of the anus which made immediate removal of the ring necessary.

Eleven children were treated by the ambulatory method with injections of quinine and urea hydrochloride. There have been no recurrences. In 3 children on digital examination a certain rigidity of the wall of the rectum above the sphincter could be demonstrated. In 3 cases a second injection within two weeks of the first became necessary.

In conclusion, I may say that I prefer the injection treatment, particularly because it may be done with the patient's remaining ambulatory. The ring method of Thiersch has—in spite of the fact that no recurrences developed—the disadvantage of hospitalization, relatively frequent inflammation and, in a few children, an extreme and permanent narrowing of the anal canal as long the ring stands intact.

SUMMARY

A description is given of the frequent occurrence of external anorectal prolapse in children during the war years. The treatment with the ring method of Thiersch and the treatment with injections of quinine and urea hydrochloride are discussed.

St. Annastraat 287.

PROPHYLAXIS OF WHOOPING COUGH

MAX J. FOX, M.D.
AND
REUBEN SNARTEMO, M.D.
MILWAUKEE

IN THE study of any disease, periodic analysis of past experience is always of value in determining the adequacy of current trends in prophylaxis and treatment. Such an analysis in the case of whooping cough leads directly to the controversial question of when prophylaxis should be attempted. In 1944, Fox and Knott [1] reported the mortality occurring at the South View Isolation Hospital in Milwaukee and emphasized the importance of early active immunization. In this paper we shall analyze the statistics from this hospital for the past sixteen years to support further our contention that immunization before 6 months of age, while it may not be as successful as that undertaken later, is often necessary as a life-saving measure. Further, we shall review recent studies on early prophylaxis showing that such immunization is clinically successful.

REVIEW OF THE LITERATURE ON PROPHYLAXIS

A brief review of the pertinent literature concerning immunization against whooping cough reveals that in 1931 pertussis vaccines were omitted from "New and Nonofficial Remedies" after a seventeen year period of acceptance. A wide variety of vaccines which were prepared improperly and administered in inadequate dosages had contributed to a more or less disappointing clinical record and this renunciation. In 1933, following important contributions by Madsen [2] and Leslie and Gardner,[3] a more effective vaccine was produced by Sauer,[4] the

From the Department of Internal Medicine, Marquette University School of Medicine, and the South View Isolation Hospital.

1. Fox, M. J., and Knott, E. A.: Whooping Cough Mortality, J. Pediat. **24**:671 (June) 1944.

2. Madsen, T.: Vaccination Against Whooping Cough, J. A. M. A. **101**:187 (July 15) 1933.

3. Leslie, P. H., and Gardner, A. D.: Phases of Haemophilis Pertussis, J. Hyg. **31**:423 (July) 1931.

4. Sauer, L. W.: Whooping Cough: A Study in Immunization, J. A. M. A. **100**:238 (Jan. 28) 1933; Immunization with Bacillus Pertussis Vaccine, ibid. **101**:1449 (Nov. 4) 1933; Municipal Control of Whooping Cough, ibid. **109**:487 (Aug. 14) 1937.

use of which enabled him to report extremely encouraging results in 1933 and again in 1937. Kendrick and Eldering,[5] using their own vaccine, were able to report good results in a large series of cases, and Mishulow and his co-workers[6] prepared a "toxin vaccine" which brought forth other favorable reports.

In a period which was critical of the use of pertussis vaccine, a general acceptance of the belief that young infants would not respond adequately to an antibody stimulus led most workers to attempt immunization during the latter half of the first year. Sauer,[7] however, did compare results in the success of immunization in a group 3 months of age and a group 6 months of age. The subsequent incidence of communicability and protection of the group 3 months of age, which could well have been viewed with enthusiasm, was overshadowed by a more striking reduction in the incidence of communicability in the group 6 months of age. It was, therefore, not surprising that in a comprehensive survey of prophylaxis of whooping cough by Hemophilus pertussis vaccines, prepared by Felton and Willard[8] and adopted for publication by the Council on Pharmacy and Chemistry of the American Medical Association in 1944, little was said about the age at immunization, except to state in conclusion that

> . . . studies . . . demonstrate that whole bacterial vaccines prepared from virulent phase I H. pertussis given in proper dosage after 6 months of age do confer significant protection as measured by reduction in the attack rate and severity of pertussis.

In regard to earlier immunization, several studies done in recent years have been extremely encouraging. Sako and his associates[9] gave three monthly immunizing injections to 3,793 infants, beginning these injections between 2 and 12 weeks of age. Monthly follow-up rapid slide agglutination tests three to four months following completion of the immunizations indicated that about 75 per cent of these infants showed positive agglutination reactions and that most of these (63 per cent) maintained their positive titers for at least two years. While the agglutinin titers are merely an indication of the infants' response, the clinical follow-up study indicated definite protection. One hundred

5. Kendrick, P., and Eldering, G.: A Study in Active Immunization Against Pertussis, Am. J. Hyg. **29**:133 (May) 1939.

6. Mishulow, L.; Mowry, I. W., and Scott, E. B.: Pertussis Toxic Filtrates and Toxin Vaccines, J. Immunol. **19**:227 (Aug.) 1930.

7. Sauer, L. W.: The Age Factor in the Active Immunization Against Whooping Cough, Am. J. Path. **17**:719 (Sept.) 1941.

8. Felton, H. M., and Willard, C. Y.: Current Status of Prophylaxis by Hemophilus Pertussis Vaccine, J. A. M. A. **126**:294 (Sept. 30) 1944.

9. Sako, W.; Trenting, W. L.; Witt, D. B., and Nichamin, S. J.: Early Immunization Against Pertussis with Alum Precipitated Vaccine, J. A. M. A. **127**:379 (Feb. 17) 1945.

and fifty-nine of these immunized infants had intimate familial exposure to whooping cough, and the incidence of the disease was only 18.9 per cent. The disease, when it did occur, was mild and no deaths resulted. No cases occurred in infants with strongly positive agglutination reactions. This contrasts sharply to the 149 similarly exposed nonimmunized controls who showed an incidence of the disease of 85.2 per cent, a severer form of the infection and a mortality of 10.2 per cent. It was also observed that these young infants tolerated the inoculations better than did the older infants and children. Waddell and L'Engle [10] attempted an even earlier immunization. One hundred and twenty-nine infants were given three injections between 1 and 8 weeks of age, and agglutinin titers at the early age of 9 weeks showed apparently adequate titers in 70 per cent of these infants, with most titers rising with increasing age; in only 1 of these did the follow-up agglutinin response seem inadequate. Again, reactions were felt to be less severe and less frequent than in older infants. The authors concluded that a satisfactory immunization response can be regularly expected when the first dose of pertussis vaccine is administered in the neonatal period.

Halpern and Halpern [11] gave a series of inoculations to 117 infants, beginning usually at the age of 4 weeks and terminating between the third and sixth month, and observed that every infant thus immunized demonstrated either a positive agglutination reaction or a positive cutaneous reaction (Flosdorf) or both. Di Sant'Agnese [12] inoculated 198 infants with a triple vaccine (diphtheria, tetanus and pertussis) at 1, 5 and 9 weeks of age. One month after the third inoculation, all infants had "protective" tetanus antitoxin levels, 84 per cent had "protective" diphtheria antitoxin levels (a subsequent booster dose raised this to 99 per cent) and about 60 per cent had "protective" pertussis agglutinin levels. The authors concluded that newborn infants do produce antibodies in response to antigenic stimuli.

In 1934, Bennholdt-Thomsen [13] reported that the pregnant rabbit when inoculated with pertussis vaccine formed antibodies which were

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10. Waddell, W. W., Jr., and L'Engle, C. S., Jr.: Immune Response to Early Administration of Pertussis Vaccine, J. Pediat. **29**:487 (Oct.) 1946.

11. Halpern, S. R., and Halpern, D.: Early Whooping Cough Immunization, J. Pediat. **33**:43 (July) 1948.

12. di Sant'Agnese, P. A.: Combined Immunization Against Diphtheria, Tetanus and Pertussis in Newborn Infants: I. Production of Antibodies in Early Infancy, Pediatrics **3**:20 (Jan.) 1949; II. Duration of Antibody Levels: Antibody Titers After Booster Dose; Effect of Passive Immunity to Diphtheria on Active Immunization with Diphtheria Toxoid, ibid. **3**:181 (Feb.) 1949.

13. Bennholdt-Thomsen, C.: Das Verhalten eines gegen den Bordet-Gengou-Bacillus spezifischen Amboceptors bei Mutter und Kind, Ztschr. f. Kinderh. **57**:532, 1934.

transmitted to the fetus. Weichsel and Douglas [14] performed complement fixation tests for whooping cough in 20 normal pregnant women and observed that only 3 of these had positive reactions but that the corresponding cord serums gave almost identical reactions, thus suggesting that specific antibodies against H. pertussis passed through the placenta. In 1937, Bradford and Slavin [15] studied the opsonocytophagic reaction of the blood in whooping cough and noted that a high titer in the newborn infant is invariably associated with a high titer in the mother. Lichty, Slavin and Bradford [16] then attempted to protect infants from whooping cough by immunizing the pregnant mothers, with little demonstrable success. These disappointing results were later explained by Cohen and Scadron,[17] who stated that the vaccinations had been done too close to term and the vaccine given in too low dosage to be effective. It was also noted that the test for phagocytosis has limitations. Cohen and Scadron inoculated 167 pregnant women in the last trimester of pregnancy, and the serums from 29 per cent of these women, as well as that of their babies, were studied by agglutination, complement fixation and mouse protection tests as done by Mishulow and his associates.[18] The authors stated that in every mother the protective titer was raised to a high level, which was almost quantitatively transmitted to the baby.

It was felt that these babies were born with a passive immunity which lasted a few weeks to a few months, while only a small percentage of babies of nonimmunized mothers could claim such protection. Opsonic studies by Kendrick, Thompson and Eldering [19] again illustrated the placental transfer of circulating antibodies to pertussis, and, in 1946, further studies were published by Cohen and Scadron,[20] who

14. Weichsel, M., and Douglas, H. S.: Complement Fixation Tests in Pertussis, J. Clin. Investigation **16**:15 (Jan.) 1937.

15. Bradford, W. L., and Slavin, B.: Opsono-Cytophagic Reaction of the Blood in Pertussis, J. Clin. Investigation **16**:825 (Sept.) 1937.

16. Lichty, J. A., Jr.; Slavin, B., and Bradford, W. L.: Attempt to Increase Resistance to Pertussis in Newborn Infants by Immunizing Their Mothers During Pregnancy, J. Clin. Investigation **17**:613 (Sept.) 1938.

17. Cohen, P., and Scadron, S. J.: Placental Transmission of Protective Antibodies Against Whooping Cough by Inoculation of Pregnant Mother, J. A. M. A. **121**:656 (Feb. 27) 1943.

18. Mishulow, L.; Siegel, M.; Leifer, L., and Berkey, S. R.: Study of Pertussis Antibodies: Protective, Agglutinating and Complement-Fixing Antibodies in Patients with Pertussis, Persons Exposed to Pertussis and Persons with No Known Exposure, Am. J. Dis. Child. **63**:875 (May) 1942.

19. Kendrick, P.; Thompson, M., and Eldering, G.: Immunity Response of Mothers and Babies to Injections of Pertussis Vaccine During Pregnancy, Am. J. Dis. Child. **70**:25 (July) 1945.

20. Cohen, P., and Scadron, S. J.: Effects of Active Immunization of Mother upon Offspring, J. Pediat. **29**:609 (Nov.) 1946.

advocated immunization against diphtheria and whooping cough during the last trimester of pregnancy to correct demonstrable immunologic deficiencies in the mother.

STATISTICAL STUDY

From Jan. 1, 1933 to Dec. 31, 1948 there were 37,774 cases of whooping cough among the residents of the city of Milwaukee. The incidence of the disease followed a rough cyclic pattern, with peaks occurring every four to five years. Increased mortality rates did not occur in the years of higher incidence. Indeed, the determinant which was of greatest significance was the patient's age. The extreme disproportion in the mortality rates between early infancy and later childhood is most strikingly illustrated by the fact that while children in the first year of life account for only 7.85 per cent of the total number of cases reported (2,966 of 37,774), they provided 72.4 per cent of the deaths (71 of 98). This is graphically illustrated in figure 1.

Fig. 1.—Graph illustrating extreme disproportion between percentages for incidence of whooping cough and deaths due to the disease in children under 1 year of age. The left column represents percentage of cases and the right column the percentage of deaths. Of 37,774 cases of whooping cough seen from 1933 to 1948, only 2,966, or 7.85 per cent were in children under 1 year of age. Of 98 deaths from whooping cough in these years, 71, or 72.45 per cent, were in children under 1 year of age.

Further demonstration of the fact that mortality rates vary inversely with the age of the patient can be seen by studying figures 2 and 3. Figure 2 represents all deaths from whooping cough occurring at South View Hospital during the years 1933 to 1948, inclusive. Analysis of these figures shows that of 36 deaths, 13 (36 per cent) occurred in infants under 3 months of age, 15 (41.7 per cent) in infants under 4 months of age and 19 (52.8 per cent) in infants under 6 months of age. In 1941, the Milwaukee Health Department began to record deaths from whooping cough by age in months. An analysis of 34 deaths occurring in the entire city of Milwaukee for the years 1941 to 1948, inclusive, as shown in figure 3, reveals that 8 deaths (23.8 per cent) occurred in infants under 3 months, 13 (38.2 per cent) in infants under 4 months, 17 (50 per cent) in infants under 6 months and 27 (79.4

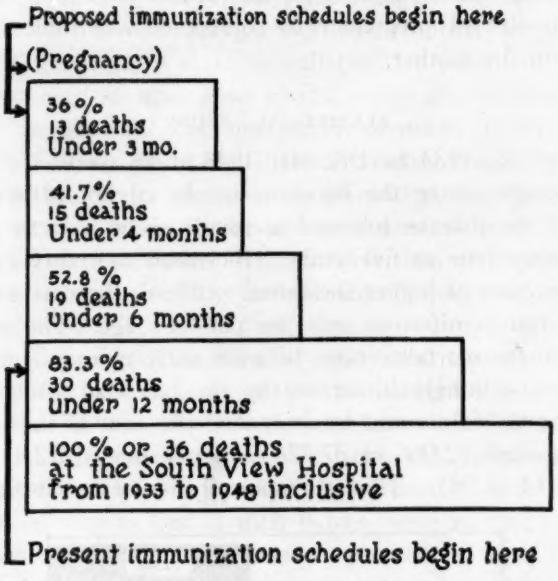


Fig. 2.—Analysis of all deaths from whooping cough occurring at South View Hospital from 1933 to 1948, with reference to immunization schedules.

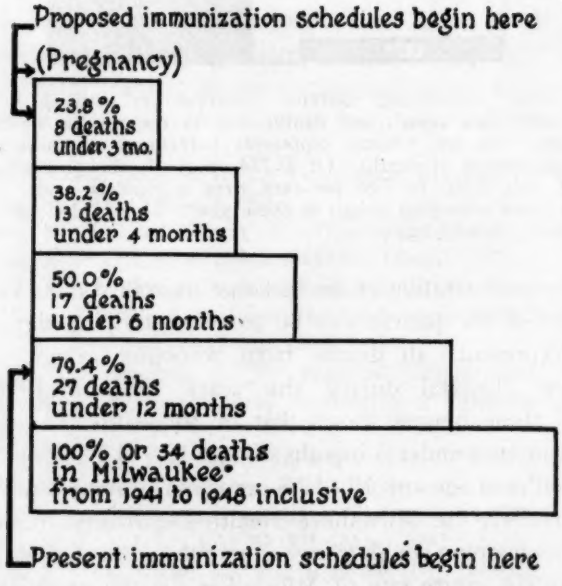


Fig. 3.—Analysis of all deaths of children under 1 year of age from whooping cough in Milwaukee from 1941 to 1948, with reference to immunization schedules.

per cent in those under 12 months of age. Dauer [21] reported that 40 per cent of all deaths from whooping cough occurred in infants under 5 months of age and 64.2 per cent in those under 1 year. However, his data are based on figures from a national survey in which the death rate in older children is higher because of inadequate medical care in rural areas, thus lowering the percentage figures for deaths in the infant group.

The mortality rate in children hospitalized at South View Hospital is seen to be over seven and a half times as great in those under 1 year of age as in those over 1 year old, with 52.8 per cent of the deaths occurring in infants under 6 months of age. Furthermore, citywide mortality statistics do not vary greatly from those of the hospital. During the past five years in Milwaukee, only 2 deaths from whooping cough have occurred in infants between the ages of 1 and 2 years, and there have been no deaths in children over the age of 2 years. It is also significant that Litvak and his co-workers,[22] in reviewing 40 cases of cerebral complications in whooping cough, observed that 50 per cent of the patients in whom these complications developed were under 1 year of age.

COMMENT

We may safely state that the age group most vulnerable to this disease is not protected by present prophylactic measures, and the question arises of how present immunization schedules may be altered in order to bring about a decrease in mortality due to whooping cough. It is extremely important to know in what manner adequate protection can be extended to children in this age group of early infancy, especially to those in the first six months of life. We have noted that it is the children of this age group who account for approximately half of the deaths due to whooping cough. This group can hardly be protected by immunizations which do not begin until the sixth month, and the problem crystallizes into the question of how early the immunization procedure can begin to call out an active immunity and offer some valuable degree of clinical protection.

While it is apparent from the table and figures 2 and 3 that the young infant falls into the highest mortality group, it is also to be noted that even in children of the youngest age group, those under 1 month of age, the mortality rate was not 100 per cent. Thus, it is shown that while the antigen-tissue clash may be severe and, at times, overwhelming, most infants manifest sufficient function of the reticuloendothelial system to survive. This would then indicate that successful

21. Dauer, C. C.: Reported Whooping Cough Morbidity and Mortality in the United States, Pub. Health Rep. **58**:661 (April 23) 1943.

22. Litvak, A. M.; Gibel, H.; Rosenthal, S. E., and Rosenblatt, P.: Cerebral Complications in Pertussis, J. Pediat. **32**:357 (April) 1948.

immunizations could be done at an early age. While the earlier studies of Sauer [23] did not produce striking success in protecting the young infants from contracting whooping cough when compared with the results obtained in older infants, they did indicate that some degree of immunity must have been conferred in many of these infants. It must also be remembered that these studies employed a vaccine of somewhat different strength than is commonly used today and that

Distribution of Whooping Cough in Children by Ages at the South View Hospital, 1933 to 1948

Children Less Than One Year of Age			
Age, Mo.	No. of Cases	No. of Deaths	Per Cent of Deaths
Under 1	11	3	27.3
1 to 2	44	7	15.9
2 to 3	21	3	14.3
3 to 4	36	2	5.6
4 to 5	25	4	16.0
5 to 6	24	0	00.0
6 to 7	19	5	26.3
7 to 8	13	1	7.7
8 to 9	7	0	0.0
9 to 10	16	1	6.3
10 to 11	13	2	15.4
11 to 12	15	2	13.3
Total	244	30	12.3

Children More Than One Year of Age			
Age, Yr.	No. of Cases	No. of Deaths	Per Cent of Deaths
1 to 2	104	1	0.96
2 to 3	63	0	0.0
3 to 4	71	1	1.4
4 to 5	47	2	4.3
5 to 6	34	1	2.9
6 to 7	30	1	3.3
7 to 8	16	0	0.0
8 to 9	10	0	0.0
9 to 10	5	0	0.0
10 to 11 and over	4	0	0.0
Total	384	6	1.6

Total no. of cases	628
Total no. of deaths	36
Mortality	5.73%

the results obtained were necessarily known only through the use of postcard questionnaires.

We should certainly agree that an immunization response is more readily obtained after 6 months of age than during the first few weeks of life, but at the same time we must point out that the percentage response and the degree of response, even in the very young infant, are at times life saving. We know from everyday practice, and it has been pointed out more specifically in the studies of Sako and his associates,[9] that those children under 6 months of age who contract whooping cough after being immunized tend to have only a mild form

23. Footnotes 4 and 7. Sauer, L. W., and Markley, E. D.: Whooping Cough: Pertussis Agglutinogen Skin Test After Immunization with Hemophilus Pertussis Vaccine, J. A. M. A. **131**:967 (July 20) 1946.

of the disease. Whether initial efforts at immunization begin at 3 months of age, at 1 week or in the pregnant mother should depend, not on a worldwide, nationwide or statewide policy, but on local immunization schedules especially fitted to suit individual circumstances. In children whose home environment is such that they can be sheltered from the common infections, the physician may well wait with their immunization program until the sixth month, when a high degree of success may be expected. When a probable exposure can be anticipated, however, as it can in crowded districts and where high rates of incidence of whooping cough prevail, then to wait until the sixth month to give infants protection is often to have waited too long. In such situations early immunization is imperative. Subsequent booster doses would then serve to prolong and reenforce the immunity obtained. Furthermore, such early immunization programs are made considerably more attractive by the fact that we have a reliable agglutinogen skin test (Flosdorf) which not only is helpful in differentiating the immune from the nonimmune but also tends to produce a prompt recall of any potential antibacterial immunity.[24]

Whooping cough is still a serious problem. Indeed, Dauer [21] stated of whooping cough:

> Its relative importance as a cause of death at the present time may be judged by the fact that it causes more deaths in children under 2 years of age than any other acute infection with the exception of pneumonia and the diarrheas.

The figures from our present study offer convincing proof that the seriousness of the disease is multiplied when it occurs in the young infant.

CONCLUSIONS

We believe that an immunization program can and should be a flexible weapon to be used according to the demands of the situation. The need for protection is directly proportional to the expected exposure. Immunization in the sixth month may be adequate in the most regulated environments, while increasingly earlier protection, extending even from the day of birth, is necessary as the environment becomes less protective. Local statistics of incidence and mortality offer a useful guide to time when immunization should be performed.

SUMMARY

1. Whooping cough continues to be an important cause of death in infancy.

2. Approximately half of the deaths from whooping cough occur in infants who have not reached the age at which immunization schedules become operative.

3. Several of the studies relating to early active and to passive immunization are reviewed.

324 East Wisconsin Avenue (2).

PROTHROMBIN STUDIES ON THE BLOOD OF THE PREMATURE INFANT AND THE VALUE OF VITAMIN K THERAPY

HEYWORTH N. SANFORD, M.D.
MARY KOSTALIK, M.D.
AND
BETSY BLACKMORE, M.D.
CHICAGO

IT HAS BEEN assumed for many years that the premature infant suffered more from hemorrhagic disturbances than the full term infant and that the premature infant's blood was even more deficient in prothrombin. For this reason, it is customary for most physicians to administer some form of vitamin K to the premature infant as prophylaxis for hemorrhagic manifestations. Actually, the literature contains comparatively meager references to the behavior of prothrombin in the premature infant. Furthermore, in only a few instances are these reports founded on any series of any considerable size, and in numerous instances the results have been contradictory on many essential points.

The first observations on the prothrombin content of the blood of the premature infant were made by Hellman and Shettles [1] in 1939. In 17 premature infants, these authors, using the two stage method of prothrombin determination, found that the prothrombin content of the blood of the premature infant was higher than that of the full term infant. Waddell and Lawson [2] a year later recorded the same observations on 23 premature infants. Kato and Poncher [3] in this same year (1940) in 73 premature infants reported the results the same as in the full term infant for the second and third days of life but somewhat lower for the remainder of the newborn period. Rouhunkoski and

From the Department of Pediatrics, Presbyterian Hospital, Rush-Presbyterian Division of the University of Illinois.

1. Hellman, L. M., and Shettles, L. B.: Factors Influencing Plasma Prothrombin in Newborn Infant: Prematurity and Vitamin K, Bull. Johns Hopkins Hosp. **65**:138, 1939.

2. Waddell, W. W., Jr., and Lawson, G. M.: Hemorrhagic Diathesis in the Newborn: Further Observations Concerning Prevention and Treatment, J. A. M. A. **115**:1416 (Oct. 26) 1940.

3. Kato, K., and Poncher, H. G.: Prothrombin in the Blood of Newborn, Mature and Immature Infants as Determined by a Micro Prothrombin Test, J. A. M. A. **114**:749 (March 2) 1940.

Saksela [4] reported the prothrombin content lower in the premature infant than in the full term infant in 15 instances. Sterner,[5] in 73 determinations, found it lower the first day and afterward the same as in the full term infant, while Oehler,[6] in 46 premature infants, observed it to be the same as in the full term infant, as did Broman [7] and Huber and Shrader.[8] This review of the literature up to 1944 shows two workers stating that the prothrombin was higher in the premature than in the full term infant, three workers stating that it was lower and three stating that there was no difference.

In 1944, Magnuson [9] made an excellent contribution to this problem. He determined the prothrombin content of the blood of 94 premature infants and compared these results with prothrombin determinations on a similar number of full term infants. He also correlated season of the year, type of delivery and method of feeding of the two groups. His observations were that, in general, the prothrombin content of the blood of the premature infant was slightly lower than that of the full term infant. In none of these studies was any attempt made to

TABLE 1.—*Weights of Premature Infants in Study*

Weight, Gm.	No. of Infants
2,251 to 2,500	20
2,001 to 2,250	39
1,501 to 2,000	26
1,000 to 1,500	15

correlate the prothrombin content of the blood with any hemorrhagic manifestations that may have developed. As we felt that this was the crux of the entire problem, the following study was made.

METHOD

One hundred premature infants were used in the study, which covered a period of eighteen months. All these infants except 5 were cared for in our nursery for premature infants. This nursery consists of individually isolated units for each premature infant, and each unit is individually heated, air conditioned and oxygenated. All the premature infants were on a four hour feeding schedule and were fed by gavage, beginning twenty-four hours after birth, a

4. Rouhunkoski, M., and Saksela, N.: Vitamin K and Prothrombin Content of Blood of the Newborn, Nord. med. **12**:3007, 1941.

5. Sterner, L. G.: Protrombinstudier hos barn med födelsevikt under 2,500 g., Nord. med. **16**:3473, 1942.

6. Oehler, E.: Die Blutgerinnungs- und die Prothrombinzeit bei Frühgeburten, Monatsschr. f. Kinderh. **90**:394, 1942.

7. Broman, B., cited by Lichtenstein, A.: K-vitaminent från pediatrisk synpunkt, Nord. med. **11**:2637, 1941.

8. Huber, C. P., and Shrader, J. C.: Blood Prothrombin Level in Newborn, Am. J. Obst. & Gynec. **41**:566, 1941.

9. Magnuson, J. H.: Studies on Prothrombin, Ann. pædiat. **163**:105, 1944.

mixture of equal parts pooled breast milk and lactic acid milk. The weights of the infants (table 1) varied between 2 and 5 pounds (1,000 to 2,500 Gm.).

Eighty-three of these infants were given no vitamin K in any form; it was given neither to the mother before the birth of the infant nor to the child after birth. These babies were all delivered in the hospital in which the nursery for premature infants is located.

Of the remaining 17 infants, 12 were delivered in other hospitals and brought to our nursery for premature infants by the Chicago Department of Health in a heated ambulance for premature babies within twenty-four hours after birth. The remaining 5 infants were delivered at the Cook County Hospital and remained in its nursery for premature babies. All these premature infants received ample vitamin K (2 to 5 mg.) immediately after birth, and almost all their mothers had also received vitamin K before delivery.

Prothrombin determinations were made on 3 cc. of venous blood plasma by the method of Quick. Blood was drawn from those infants born in our hospital

TABLE 2.—*Prothrombin Determinations*

	Group Not Given Vitamin K			Group Given Vitamin K		
Day of Life	No. of Infants	Prothrombin, % of Normal	% of Error	No. of Infants	Prothrombin, % of Normal	% of Error
1	28	73	±6.4	11	80	±4.1
2	64	62	±6.6	12	65	±4.2
3	70	55	±6.8	13	81	±4.4
4	68	72	±6.9	10	84	±4.4
5	64	74	±5.7	9	60	±4.5
6	66	75	±6.4	8	73	±4.1
7	68	80	±6.2	8	75	±4.0
8	66	77	±6.4	8	75	±4.2
9	66	70	±4.9	8	71	±4.1
10	42	80	±4.8	8	78	±4.1
11	50	83	±6.1	7	88	±2.9
12	42	88	±4.9	7	90	±4.0
13	42	90	±6.1	7	85	±2.9
14	46	85	±6.4	..	..	.....
15	48	88	±6.6	..	..	.....
16	52	88	±4.9	..	..	.....
17	46	91	±6.1	..	..	.....
18	34	88	±3.8	..	..	.....

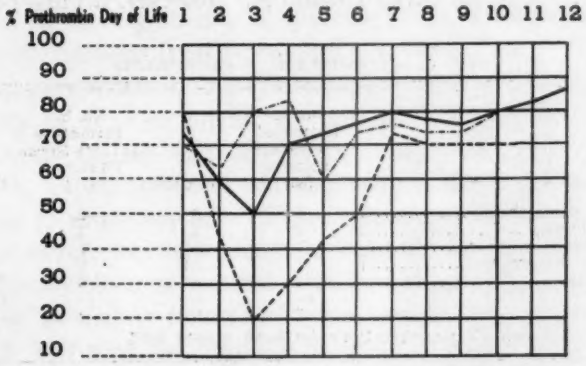
immediately after birth and from those born in outside hospitals as soon as they were admitted to our nursery. This blood was drawn within the first twenty-four hours of life. Prothrombin levels on no premature infant's blood were included in this study that were not estimated for at least five consecutive days, the only exception being the data on those infants who died within this period. If these infants had manifested hemorrhagic disturbances of any kind, their blood prothrombin levels were included in this study.

RESULTS

There was no apparent correlation between time of gestation, weight or type of feeding and the amount of prothrombin found in the blood. That is to say, while after the first forty-eight hours the feeding of all the infants was similar, before that time the feeding might or might not have been started and varied somewhat for those infants delivered in other hospitals. This had no apparent effect on the amount of prothrombin found in the blood. Also, the age of gestation in months

as estimated by the weight at birth apparently made no difference in the amount of prothrombin observed. A child of 1,000 Gm. (approximately 2 pounds) had exactly the same prothrombin content of the blood as one weighing 2,500 Gm. (approximately 5.5 pounds).

There was some variation in prothrombin content of the blood among individual infants (table 2). The statistical correction for error varied between ± 3.8 and ± 6.9 per cent. The curve shown for prothrombin content (chart) is the median average for each day of life. The average prothrombin content of the blood of the premature infant was about the same as that of the full term infant at birth and decreased similarly for the first three days of life. However, this decrease was less than that of the full term infant; the decrease to the third day of life was 50 per cent as compared with 20 per cent for



Graph showing prothrombin values for premature infants. Those for normal infants are indicated by a broken line, those for premature infants not given vitamin K, by a solid line, and those for premature infants given vitamin K, by a line of dots and dashes.

the full term infant, the average curve for the newborn period in the full term infant being taken from similar studies in 1942.[10]

The increase in prothrombin content of the blood was also more rapid than in the full term infant, the value being nearly that at birth (70 per cent) by the fourth day of life and steadily rising thereafter to 80 per cent by the eighth day of life, whereas the full term infant does not show an increase to 70 per cent for the prothrombin content of the blood until the seventh day of life. In the full term infant the prothrombin content does not increase much beyond this level throughout the remainder of the newborn period.

In those premature infants given vitamin K the early decrease in prothrombin content of the blood did not occur, the level falling only

10. Sanford, H. N.; Shmigelsky, I., and Chapin, J. M.: Is Administration of Vitamin K to the Newborn of Clinical Value? J. A. M. A. **118**:697 (Feb. 28) 1942.

to 65 per cent on the second day of life and increasing to 80 per cent on the third day. There was a drop to 60 per cent on the fifth day of life, then a rise to the same level as that of the premature infant given no vitamin K. It may be seen, therefore, that the administration of vitamin K increased the prothrombin content of the blood during the early days of life in the premature infant as in the full term infant.[10]

COMMENT

While the administration of vitamin K to the premature infant increased the prothrombin content of the blood, it had no observable clinical effect on the hemorrhagic manifestations, just as in the full term infant [10] (table 3). There were 6 per cent with hemorrhagic manifestations in the untreated group of premature infants as compared with 24 per cent in the group given vitamin K. However, it must be remem-

TABLE 3.—*Hemorrhagic Manifestations*

Type	No. in Untreated Premature Infants (83)	Per Cent	No. in Premature Infants Given Vitamin K (17)	Per Cent
Cerebral hemorrhage	0	0	2	12.0
Melena (bowel)	2	2.4	1	6.0
Hematemesis	1	1.2	1	6.0
Umbilical hemorrhage	1	1.2	0	0
Ecchymosis	1	1.2	0	0
Total	5	6.0	4	24.0

Total hemorrhagic manifestations for both groups 9.0%

bered that the group of premature infants who were treated with vitamin K had had considerably more manipulation during delivery and transportation than the untreated group. These figures simply demonstrate that capillary fragility is an important factor in the premature infant and that the administration of vitamin K does not materially affect the hemorrhage once it has begun. The average number of hemorrhagic manifestations for both groups was 9 per cent, as compared with 6.6 per cent for the full term infant.

One observation interesting to us was the absence of retinal hemorrhages in both groups of premature infants. Thirty-five per cent or more of full term infants will show retinal hemorrhages during the first days of life. The eyes of all the premature infants in both groups were examined as soon as possible after birth, since we were also studying retrolental fibroplasia. This was done by one of us (H. N. S.), and the observations were checked by Dr. Justin M. Donegan, our ophthalmologist, yet no retinal hemorrhages were seen in either group.

There was a total of 5 premature infants in the untreated group who showed hemorrhagic manifestations (table 3). Two infants exhib-

ited melena (blood in the stool) on the first and second days of life. There were no further symptoms. The prothrombin content of the blood was within normal limits in both babies. One infant vomited bright red blood on the first and second days of life. No treatment of any kind was given and no further disturbances were noted. The prothrombin content of the blood was 72, 58 and 52 per cent for the first three days of life, and increased to 70 per cent thereafter. One infant had several areas of ecchymosis on the arms and legs on the second day of life, which condition disappeared spontaneously during the next few days. The prothrombin content of the blood was above 50 per cent for the first three days of life, increased to 75 per cent by the fourth day and continued at that level. One infant had considerable bleeding from the cord on the eighth day of life. Clinically, the bleeding was mechanical but the infant is included in this group. The prothrombin content of the blood on the eighth day of life was within normal limits (82 per cent), as it had been from birth until this time.

There were 4 infants with hemorrhagic manifestations in the group given vitamin K. One infant had melena (emesis of blood and blood in the stool) on the first day of life and died on the second day. Permission for autopsy was not obtained. Vitamin K had been given this infant in ample amounts (5 mg. subcutaneously) immediately after birth. However, we were unable to estimate any prothrombin content in this infant's blood or to obtain clot formation. This will be discussed later. One premature infant had some hematemesis on the second day of life; at this time the prothrombin content of the blood was 82 per cent. Two premature infants died of cerebral hemorrhage on the third and fourth days of life, respectively. One had been given 5 mg. of vitamin K immediately after birth. The prothrombin values of their blood were well within normal limits: 72 and 65 per cent on the second and third days of life and, for the second infant, 50 per cent on the fourth day of life four hours before death.

The effect of the administration of vitamin K on the total mortality of the premature infants is shown in table 4. There was almost four times the mortality among premature infants given vitamin K as among those untreated. It will be observed in both groups of premature infants that 90 per cent of the total mortality occurred in the first forty-eight hours of life. No hemorrhagic manifestations occurred in either group as shown by careful observation at autopsy except for the two cerebral hemorrhages in the group given vitamin K. In both these infants there were asphyxial disturbances that were probably more a cause of death than the cerebral hemorrhage.

We wish to emphasize that the great difference in mortality between the two groups is in no way due to the administration of vitamin K. Those infants given vitamin K were born outside our hospital, under

poor conditions of delivery and care. This is the cause of the difference. Our studies simply indicate that the administration of vitamin K had no effect one way or the other on the mortality. Mortality of premature infants is greatly influenced by immediate care. For years, the mortality of premature infants born outside this hospital has been three to four times greater than that of those born within the hospital. The same reasoning applies to the greater number of cerebral hemorrhages in the treated group. We have always believed that cerebral hemorrhage is not particularly influenced by the speed of blood coagulation. All our studies show in this respect is that even when vitamin K is given at once and in ample amounts, cerebral hemorrhage occurs

TABLE 4.—*Mortality of Premature Infants During Study*

Untreated Premature Infants (Not Given Vitamin K) 83				Premature Infants Given Vitamin K, 17			
	Weight				Weight		
Lived	Pounds	Ounces	Cause of Death as Seen at Autopsy	Lived	Pounds	Ounces	Cause of Death as Seen at Autopsy
1 hr.	1	14	Atelectasis	10 hr.	3	2	Atelectasis
3 hr.	2	4	Atelectasis	18 hr.	5	1	Atelectasis and emphysema of lung
9 hr.	1	9	Atelectasis				
10 hr.	3	6	Atelectasis and aspiration of amniotic fluid	32 hr.	1	12	Atelectasis and aspiration of amniotic fluid
				33 hr.	2	14	Atelectasis and bronchopneumonia
14 hr.	2	4	Congenital defects				
15 hr.	5	½	Fetal endocarditis	36 hr.	2	9	Bacteremia (S. viridans)
18 hr.	2	14	Atelectasis and aspiration of amniotic fluid	48 hr.	3	8	Atresia of esophagus
				50 hr.	2	3	Asphyxia and aspiration of amniotic fluid; hemorrhage into lateral ventricle
22 hr.	2	8	Atelectasis and aspiration of amniotic fluid				
23 hr.	1	7	Atelectasis and bronchopneumonia	4 days	2	10	Atelectasis and aspiration of amniotic fluid; subarachnoid hemorrhage
8 days	4	8	Congenital defects; pulmonary abscess				
Total 10 deaths (12 per cent mortality)				Total 8 deaths (47 per cent mortality)			

just the same. Whether the vitamin would decrease the amount of the bleeding once the vessel has been ruptured, we cannot say. In these 2 instances at least, the premature infants died in spite of ample vitamin K therapy and a high prothrombin content of the blood.

There is one phase of this matter that we are unable to explain. Why do some premature infants (5 per cent) have no clot formation in their blood and no estimable prothrombin on the first day of life? This absence does not seem to make any great difference in the well-being of these infants, for while, as already mentioned, one such premature infant given vitamin K at birth died on the second day of life, 4 with no clot formation or estimable prothrombin on the first day of life had normal clot formation and normal prothrombin values on the second day. These last 4 infants were entirely normal and exhibited

no hemorrhagic manifestations of any kind. We can easily see that if a premature infant exhibited hemorrhagic manifestations the first day of life, with no clot formation or estimable prothrombin, hemorrhage due to hypothrombinemia might be suspected. However, it is seen that this peculiar finding is observable in perfectly normal infants, without any hemorrhagic manifestations at all. Magnuson [9] found 5 similar instances in his study. He observed that none of the premature infants with this low prothrombin content of the blood exhibited any pathologic symptoms and all appeared to be completely normal.

CONCLUSIONS

Prothrombin estimations were made by the method of Quick on the plasma of 3 cc. of blood from each of 100 premature infants in a study covering a period of eighteen months. Eighty-three of these premature infants were given nothing to influence their blood coagulation, neither the mother before birth nor the child after birth receiving any such preparation. The remaining 17 were given vitamin K in ample quantities, to the child immediately after birth in every instance and to the mother before birth of the child as well in many instances.

The prothrombin values were slightly higher than those reported for the full term infant for the first fourteen days of life in the untreated premature infants. There was an increase in the prothrombin content of the blood above that of the untreated infants in those premature infants given vitamin K.

However, there were just as many hemorrhagic manifestations in the premature infants given vitamin K as in the untreated group, and the mortality and frequency of cerebral hemorrhage, as shown by autopsy observations, were higher. However, this proportion of increase was due to the fact that the initial care was not as good, in general, as that of the untreated group.

Our studies indicate, therefore, that the administration of vitamin K to premature infants in an endeavor to decrease hemorrhagic manifestations is without clinical basis.

952 North Michigan Avenue.

HEREDITY IN THE INFANTILE TYPE OF GAUCHER'S DISEASE

Report of a Case

EUGENE STRANSKY, M.D.
AND
DOMICIANA F. DAUIS-LAWAS, M.D.
MANILA, PHILIPPINES

THE chronic type of kerasin storage disease has been known since 1882, when Gaucher [1] published his paper on "the primary epithelioma" of the spleen. This condition was found by Schlagenhaufer [2] in 1907 to be a systemic disease of the reticuloendothelial system, and the acute or infantile type of the disease was differentiated from the chronic or adult type in 1927 by Oberling and Woringer.[3] The term "acute Gaucher's disease" was coined by Rowland [4] in 1928 in order to distinguish it from the more chronic type in larger children and adults which was previously known. The acute or infantile type is, according to Rowland,[5] a rare form of the disease with clinical and pathologic features somewhat different from those of the chronic type. It is characterized by striking familial tendency, by the development of nervous symptoms at the age of 5 to 6 months due to progressive cerebral decortication and, in contrast to the chronic type, by short duration and early fatal termination, without pigmentation.

Reports of cases which may be considered as of the acute type of Gaucher's disease have been published by Kraus (1920),[6] Reber (1924),[7]

From the Department of Pediatrics, University of the Philippines College of Medicine.

1. Gaucher, M.: L'epitheliome primitif de la rate sans leucémie, Thesis, Paris, 1882.

2. Schlagenhaufer, F.: Ueber meist familiär vorkommende histologisch charakteristische Splenomegalien, Typus Gaucher, Virchows Arch. f. path. Anat. **87**:125, 1906-1907.

3. Oberling, C., and Woringer, P.: La maladie de Gaucher chez le nourrisson, Rev. franç. de pédiat. **3**:475, 1927.

4. Rowland, R. S.: Xanthomatosis and the Reticulo-Endothelial System, Arch. Int. Med. **42**:611 (Nov.) 1928.

5. Rowland, R. S.: Gaucher's Disease, in Brennemann, J.: Practice of Pediatrics, ed. 3, Hagerstown, Md., W. F. Prior Company, Inc., 1947, vol. 3, chap. 23.

6. Kraus, E. J.: Zur Kenntnis der Splenomegalie Gaucher, insbesondere der Histogenese der grosszelligen Wucherung, Ztschr. f. ang. Anat. **7**:186, 1920.

7. Reber, M.: Splenomegalie Gaucher im Säuglingsalter, Jahrb. f. Kinderh. **105**:271, 1924.

Harper (1926),[8] Oberling and Woringer (1927),[9] Dienst and Hamperl (1927),[9] Moncrieff (1930),[10] one of us (E. S., 1930),[11] Rusca (1931),[12] Findlay (1931),[13] Donovan (1931),[14] Winter (1932),[15] Meyer (1932),[16] Macera and Brachetto Brian (1937),[17] Aballi and Kato (1938),[18] Aballi, Sala Panicello and Pascual Gispert (1938),[19] Atkinson (1938),[20] de Lange (1939),[21] one of us (E. S.) and Pecache (1940),[22] Fernandez Tosco (1941) [23] and others whose reports we could not locate owing to our still deficient library facilities.

While the pathologic changes of Gaucher's disease were elucidated by Lieb and Mladenović [24] as early as 1924 and 1929, and again in 1930 by Epstein and Lorenz [25] who established definitely that the disease is

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8. Harper, W. W.: Splenomegaly of the Gaucher Type, South. M. J. **19**:726, 1926.

9. Dienst, G., and Hamperl, H.: Lipoidzellige Splenomegalie (Typus Niemann), Wien. klin. Wchnschr. **77**:1432, 1927.

10. Moncrieff, A.: The Infantile Type of Gaucher's Disease, Arch. Dis. Childhood **5**:265, 1930.

11. Stransky, E.: Ueber grosszellige Splenohepatomegalie, Jahrb. f. Kinderh. **126**:204, 1930.

12. Rusca, L.: Sul morbo del Gaucher, Haematologica **2**:441, 1931.

13. Findlay, L.: Gaucher's Disease Verified by Splenic Puncture, Proc. Roy Soc. Med. **28**:848, 1930-1931.

14. Donovan, E. J.: Splenectomy in a Child Eleven Months of Age for Gaucher's Disease, S. Clin. North America **11**:511, 1931.

15. Winter, S. J.: Lipoid Histiocytosis (Niemann-Pick Type), Am. J. Dis. Child. **43**:1150 (May, pt. 1) 1932.

16. Meyer, R.: Syndrome neurologique et diagnostic clinique de la maladie de Gaucher du nourrisson, Rev. franç de pédiat. **8**:559, 1932.

17. Macera, H., and Brachetto Brian, D.: Enfermedad de Gaucher en un niño de 19 meses de edad, Crón. méd., Lima **54**:256, 1937.

18. Aballi, A. J., and Kato, K.: Gaucher's Disease in Early Infancy: Review of Literature and Report of Case with Neurological Symptoms, J. Pediat. **13**:364, 1938.

19. Aballi, A.: Sala Panicello, F., and Pascual Gispert, J.: Enfermedad de Gaucher, Bol. Soc. cubana de pediat. **10**:547, 1938.

20. Atkinson, F. R.: Gaucher's Disease in Childhood, Brit. J. Child Dis. **35**:1, 1938.

21. de Lange, C.: Ueber die maligne Form der Gaucherschen Krankheit, Acta pædiat. **27**:34, 1939.

22. Stransky, E., and Pecache, L. V.: Gaucher's Disease in Early Infancy, Acta med. Philippina **2**:21, 1940.

23. Fernandez Tosco, M. A.: Enfermedad de Gaucher en un lactante, Bol. Soc. cubana de pediat. **13**:252, 1941.

24. Lieb, H.: Cerebrosidspeicherung bei Splenomegalie Typus Gaucher, Ztschr. f. physiol. Chem. **140**:305, 1924. Lieb, H., and Mladenović, M.: Cerebrosidspeicherung bei Morbus Gaucher, ibid. **181**:208, 1929.

25. Epstein, E., and Lorenz, K.: Die Phosphatidzellverfettung der Milz in Niemann-Pickscher Krankheit verglichen mit der Lipoidchemie des Morbus Gaucher und der Schüller-Christianschen Krankheit, Ztschr. f. physiol. Chem. **192**:145, 1930.

due to storage of cerebrosides in the cells of the reticuloendothelial system, not much has been known until recently of the causation or, better, the hereditary mechanism of the disease. The familial occurrence of Gaucher's disease has long been known. Collier [26] reported on the familial occurrence of the disease as early as 1895 and Bovaird [27] in 1900. Anderson [28] presented in 1933 a paper describing 3 probable cases of the disease in three sisters. One of them had nine grandchildren, 2 of whom have proved, 2, probable and 2, possible Gaucher's disease, while in the second generation there has been not a single case of the disease. As for the acute type of the disease, Oberling and Woringer [3] reported 4 cases in the same family and Woringer [29] in an additional paper in 1934 reported observations on a fifth case in the same family. The disease had so affected this family that of 7 siblings 5 died at an early age from the acute type. One of us (E. S.) [11] reported in 1930 on 3 consecutive cases of acute Gaucher's disease in the same family. All these observations were, however, not yet sufficient to prove definitely the hereditary mechanism of the disease. More recent papers have finally made it possible to obtain a clear picture of the hereditary mechanism. It has been found that in Gaucher's disease, acute or chronic, the typical foam or storage cells may be demonstrated in the bone marrow (Löwinger, 1935 [30]; Vogel, Erf and Rosenthal, 1937 [31]; Vogel and Bassen, 1939 [32]; Henning and Keilhack, 1939,[33] and Schartum-Hansen, 1938 [34]). There were even case reports on Gaucher's disease without splenomegaly, diagnosed by the presence of the Gaucher cells in the bone marrow (Petit and Schleicher [35];

26. Collier, W. A.: A Case of Enlarged Spleen in a Child Aged Six Years, Tr. Path. Soc., London **46**:148, 1895.

27. Bovaird, D.: Primary Splenomegaly–Endothelial Hyperplasia of the Spleen: Two Cases in Children, Am. J. M. Sc. **120**:377, 1900.

28. Anderson, J. P.: Hereditary Gaucher's Disease, J. A. M. A. **101**:979 (Sept. 23) 1933.

29. Woringer, P.: Cinquième enfant atteint de maladie de Gaucher dans une même famille, J. de méd. de Paris **54**:689, 1934.

30. Löwinger, S.: Die Bedeutung der Knochenmark- und Milspunktion für die Diagnose des Morbus Gaucher, Folia haemat. **53**:126, 1935.

31. Vogel, P.; Erf, L. A., and Rosenthal, N.: Hematological Observations on Bone Marrow Obtained by Sternal Puncture, Am. J. Clin. Path. **7**:436 and 498, 1937.

32. Vogel, P., and Bassen, F. A.: Sternal Marrow of Children in Normal and in Pathologic States, Am. J. Dis. Child. **57**:245 (Feb.) 1939.

33. Henning, N., and Keilhack, H.: Die Ergebnisse der Sternalpunktion, Ergebn. d. inn. Med. u. Kinderh. **56**:372, 1936.

34. Schartum-Hansen, H.: Sternalpunktion bei Morbus Gaucher, Folia haemat. **61**:180, 1938.

35. Petit, J. V., and Schleicher, C. M.: Atypical Gaucher's Disease, Am. J. Clin. Path. **13**:260, 1943.

Morgans [36]). Groen and Garrer [37] emphasized again the value of sternal puncture as an aid to the diagnosis of Gaucher's disease (1948), while Groen [38] was able to furnish proof of the hereditary mechanism of the disease by detecting Gaucher cells in the bone marrow of apparently healthy persons, the offspring of whom had manifest Gaucher's disease. On account of these findings Groen [38] could stress the fact that

> . . . the disease tended to become more severe in every succeeding generation until after two or three generations it became clinically manifest in the affected individuals early in life. In the next generation it would then establish itself during fetal life so as to give rise to abortion, stillbirth or early death of the affected infant.

Although he was able to collect 25 cases of Gaucher's disease, there was not a single one of the infantile or acute form. At any rate, Groen has the credit for discovery of the hereditary mechanism of the disease, and we are following his suggestions in furnishing evidence for the heredity of the acute type of Gaucher's disease.

REPORT OF CASES

We had the chance to observe Gaucher's disease in a brother of the patient described by one of us (E. S.) and Pecache [22] in 1940. This patient died suddenly as already reported, a few days after he was taken home against advice.

In this family the first case of Gaucher's disease was that of the first son in the family. After this son there were four more children, three of whom were living. One, also a boy, who could not be observed, died suddenly at the age of 14 months, during the enemy occupation of the province, where the family is still living. Two children, a son and a daughter, are living and doing well. The youngest child, a boy, however, had Gaucher's disease. We had the chance to examine the father and mother of the children. While the father was found to be completely normal, we were able to detect definite Gaucher cells in the bone marrow of the mother. A further interesting point in our observation is the fact that the infants seen by us did not show any nervous symptoms. All 3 patients reported on by one of us (E. S.) [11] in 1930 had definite symptoms of decortication. We know, however, from the paper of Aballi and Kato [18] that of 27 cases of acute Gaucher's disease compiled

36. Morgans, M. E.: Gaucher's Disease Without Splenomegaly, Lancet **2**:576, 1947.

37. Groen, J., and Garrer, A. H.: Adult Gaucher's Disease with Special Reference to the Variations in Its Clinical Course and the Value of Sternal Puncture as an Aid to Its Diagnosis, Blood **3**:1221, 1948.

38. Groen, J.: The Hereditary Mechanism of Gaucher's Disease, Blood **3**:1238, 1948.

from the literature (with 1 case of their own) 17 included symptoms of involvement of the central nervous system, while the remaining 10 did not. It may be that the involvement of the central nervous system is likewise due to some hereditary trait, as in the report of Woringer [29] in which all five siblings of the same family showed nervous involvement.

CASE 1 (previously published [22]).—This patient was admitted to the hospital on Nov. 22, 1939 with the chief complaints of abdominal enlargement, presence of a mass on the left side of the abdomen and pallor. There was a history of repeated respiratory infections. The present illness started three months prior to his admission, with frequency of bowel movements which lasted for one month. During this time, the mother noticed accidentally a hard mass in the left hypochondrium which increased rapidly in size. On his admission, the spleen was found to extend below the left iliac crest, the median border reaching the umbilicus. The liver was likewise enlarged, reaching 3 fingerbreadths below the right costal arch. There was severe anemia with the presence of some immature granulocytes and nucleated red cells. The bone marrow showed a decided increase of erythropoietic activity, reminding one of hemolytic anemia. As for the diagnosis, splenic puncture was done and many isolated foam cells with the cytoplasm appearing as wrinkled tissue paper were found. Sudan III staining was slightly positive; the other stains for fat gave negative results. No Gaucher cells could be found in the bone marrow of the child. Malaria could be definitely ruled out, as the child came from a malaria-free region, and there were no malarial parasites in the blood of either the mother or the child. The child stayed in the hospital until Feb. 25, 1940. He was taken home against advice, where he died suddenly four days later; no autopsy could be performed.

It has already been mentioned that a second son died at the age of 14 months during the enemy occupation, when, owing to the disrupted communication lines, the child could not be brought to the hospital. Although the mother denied any splenic enlargement in the child, it is most probable that the child likewise died of Gaucher's disease, as the death was sudden, without any premonitory symptoms as in the case of the first child. One daughter, now 9 years old, and another son, 3 years old, are well and free of the disease.

CASE 2.—The third child, likewise a boy, was admitted to the hospital on Feb. 14, 1949 with Gaucher's disease, at the age of exactly 1 year. The chief complaints were increasing pallor, fever and presence of an intra-abdominal mass. At the age of 5 months, the completely breast-fed infant had loose bowel movements, lasting for a week. At that time, the mother noticed a hard mass in the left hypochondrium, which later increased gradually in size. The child then had fever and cough from time to time. The bodily and mental development was, however, almost normal; at the age of 1 year the weight of the child was approximately 8,500 Gm. and the height, 74 cm. The child could walk without help. There were already 8 incisors. The most important observations on his admission were as follows: The spleen was palpable 3 fingerbreadths left from the umbilicus, reaching the level of the umbilical line downward. The organ was hard

and smooth. The liver was likewise enlarged, hard and smooth, reaching 2 to 3 fingerbreadths below the right costal arch. The enlargement of the spleen and liver may be seen from figures 1 and 2. Studies of the blood showed a hemoglobin concentration of 6.1 Gm. per hundred cubic centimeters, with 3,170,000 red blood cells, 11,500 white blood cells and 65,000 thrombocytes, per cubic millimeter. The hemogram showed 44.8 per cent lymphocytes, 5.6 per cent eosinophils, 4.8 per cent stab forms, 4 per cent segmented forms, 4.4 per cent monocytes and 0.4 per cent thrombocytes, with no basophils, myelocytes or juvenile forms. Moderate anisocytosis was displayed. Examination of urine and feces did not show any abnormality.

In the aspirated material from the spleen (two samples) there were many large, poorly stained cells with a relatively small peripheral nucleus of reticulo-endothelial structure and a filamentous cytoplasm resembling wrinkled tissue paper.

Fig. 1.—The child (case 2) with acute Gaucher's disease at the age of 1 year. Note enlargement of spleen and liver.

There were entire tissue fragments from the spleen showing an almost complete metaplasia composed of the aforementioned cells as described originally by Gaucher.[1] The same cells were found in the aspirated material from the liver, although they were less numerous. In figure 3 the cells seen in the spleen are reproduced. Repeated examinations of the bone marrow, however, failed to show the typical cells, although roentgenograms of the bones revealed some rarefied areas on the lower ends of both femurs. The sternal and tibial marrow was examined. It may be pointed out that we also failed nine years before to find Gaucher cells in the marrow of the brother.

The child stayed in the ward until March 8. He had normal temperatures with occasional subfebrile peaks. The hemoglobin level increased during this time from 6.1 to 7.6 Gm. per hundred cubic centimeters because of the administration of ferrous sulfate. Since almost all infants in the Philippines have iron deficiency

anemia,[39] the anemia had not much to do with the disease itself. As the mother had to take care of the other children, she was unable to stay longer in the hospital.

The observations on the mother are important. There was no splenohepatomegaly at all, nor any anemia. The bone marrow was examined twice to avoid any error. Both times there were scattered and isolated, although typical, Gaucher cells. We tried our best to get good photomicrographs of these cells, but it was almost impossible to distinguish isolated cells from the normal reticuloendothelial cells of the bone marrow in the picture. The smears have been presented to various pathologists and hematologists, who have not been able to give

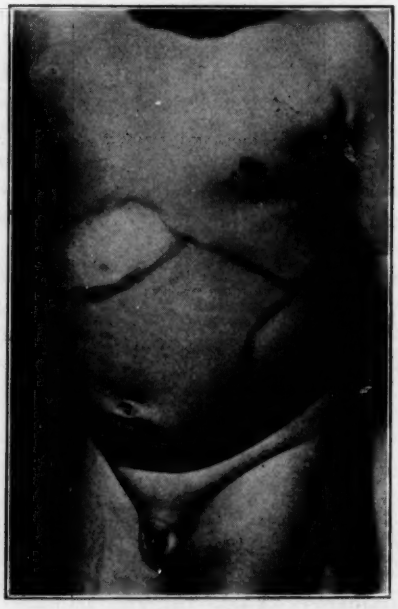

Fig. 2.—Close-up view of child (case 2) with acute Gaucher's disease showing enlargement of spleen and liver.

any further information. They reported unanimously that the cells in the marrow were definitely Gaucher cells. In this connection, the statement of Groen and Garrer [37] may be emphasized:

> Even more commonly one finds cells that are somewhat intermediary in type between the reticulum cell and Gaucher cell. They have the size of the reticulum cell, or are a little larger, the protoplasm has the faint staining of the reticulum cell but it is more meshy in structure. If they were seen in normal bone marrow one would call them reticulum cells; in the presence of typical Gaucher cells, one is inclined to regard them as small atypical Gaucher cells.

39. Stransky, E., and Dauis-Lawas, D. F.: On Iron Deficiency Anemia in Infancy and Childhood in the Tropics, Ann. pædiat. **171**:139, 1948.

This type of cell was described by Mandelbaum and Downey [40] in 1916. In our case, there were a few large Gaucher cells but many more of the "early" or "young" Gaucher cells (Groen and Garrer [37]). There were no appreciable changes in the roentgenographic appearance of the bones of the mother. We did not expect them, as a sufficient aggregation of cells to produce a rarefaction of the bones visible in roentgenograms was not probable.

Fig. 3.—Photomicrograph of cells from the spleen in child with acute Gaucher's disease (case 2).

We should like to refer here to cases 7 and 8 of Groen and Garrer.[37] Two girls had the chronic type of Gaucher's disease. The bone marrow of the mother was completely normal; that of the father, however, showed scattered, rather small and early Gaucher cells. There

40. Mandelbaum, F. S., and Downey, H.: The Histopathology and Biology of Gaucher's Disease, Folia haemat. **20**:139, 1916.

were no other findings in the girls' apparently healthy father. While these Dutch authors reported on chronic types of Gaucher's disease, we are reporting on the infantile type.

As to the question of whether there is a real difference between the infantile and adult types of Gaucher's disease in the sense that the metabolic disturbance in both types is similar or different, we believe we may rightfully answer in the negative. Ottenstein, Schmidt and Thannhauser [41] reported recently on the results of quantitative chemical examinations of the spleens in 2 instances of the infantile type of Gaucher's disease (the infants died at the ages of 7 and 5½ months, respectively) and in 4 instances of the chronic type of the disease in adults. There were no differences at all. They stated that the disease, acute or chronic, is "the result of a deviation of the intracellular metabolism of reticulum cells and histiocytes" which leads to deposits of the formed cerebrosides in the cells themselves. It is probable, however, that we are dealing with an embryonic type of disturbance of the intracellular metabolism and it is more probable that the disturbance will be more widespread in infancy than at later ages in spite of the familial occurrence and hereditary mechanism of the disease.

SUMMARY AND CONCLUSIONS

Two cases of children with verified acute Gaucher's disease are reported in one family of five siblings, while a third case is considered as probable. Both patients observed showed signs of the disease in early infancy. The first patient died at the age of 14 months, and the child with the probable condition at about the same age, while the second child with the verified case of the disease is still alive at the age of 13 months. In the patients observed there were no nervous manifestations. No Gaucher cells could be demonstrated in the bone marrow of either child. The carrier of the disease was definitely the mother of the children, in whose bone marrow typical, although relatively small and young, Gaucher cells were discovered. This report so far as we are informed is the first one on the infantile type of the disease in which the carrier of the disease could be detected; hence the report is important among the evidence for the familial occurrence, heredity and hereditary mechanism of Gaucher's disease.

41. Ottenstein, B.; Schmidt, G., and Thannhauser, S. J.: Studies Concerning the Pathogenesis of Gaucher's Disease, Blood **3**:1250, 1948.

CARDIAC ENLARGEMENT IN UNCOMPLICATED MITRAL INSUFFICIENCY IN CHILDREN

JOSEPH H. MILLER, M.D.
LOS ANGELES
AND
BERNICE G. WEDUM, M.D.
WASHINGTON, D. C.

THE criteria for the diagnosis of mitral insufficiency, as set forth by the New York Heart Association,[1] require the presence of enlargement of the heart in addition to a systolic murmur at the apex. In the opinion of some clinicians, this requirement of cardiac enlargement does not apply to children [2] or young adults.[3] The present paper reports further evidence on this matter from observations on 1,971 children seen in consultation during the first two years of operation of the Denver Area Rheumatic Fever Diagnostic Service (1944 to 1946).

METHODS

The record of each child was coded, using the punch card method of the International Business Machine Corporation. Two hundred and twenty-six of the 1,971 children examined had rheumatic heart disease. One hundred and sixty-four of the 226 had mitral insufficiency; 58 of this group also had mitral stenosis, aortic stenosis, aortic insufficiency, tricuspid insufficiency or pericarditis. An additional 21 had middiastolic murmurs and were thought to have possible early mitral stenosis. There remained 85 children in whom mitral insufficiency was

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From the Denver Area Rheumatic Fever Diagnostic Service, University of Colorado Medical Center, Denver.

1. Nomenclature and Criteria for Diagnosis of Diseases of the Heart, ed. 4, New York Heart Association, New York, New York Tuberculosis and Health Association, 1939.

2. (*a*) Gibson, S.: The Clinical Significance of Heart Murmurs in Children, M. Clin. North America **30**:35, 1946 (*b*) Kuttner, A. G., and Markowitz, M.: The Diagnosis of Mitral Insufficiency in Rheumatic Children, Am. Heart J. **35**:718, 1948. (*c*) Seham, M.; Shapiro, M. J., and Hilbert, E. H.: The Early Diagnosis of Rheumatic Heart Disease in Children, Am. J. Dis. Child. **42**:503 (Sept.) 1931. (*d*) Boone, J. A., and Levine, S. A.: The Prognosis in "Potential Rheumatic Heart Disease" and "Rheumatic Mitral Insufficiency," Am. J. M. Sc. **195**:764, 1938.

3. Parker, R. C., and White, B. V.: Aids to Evaluation of Systolic Heart Murmurs in the Selection of Naval Personnel, U. S. Nav. M. Bull. **42**:87, 1944.

the only rheumatic lesion. The charts of 3 children were incomplete and were discarded. Data on the remaining 82 patients are the basis of the present paper.

The diagnosis of mitral insufficiency was made in the presence of a long, blowing systolic murmur, varying in intensity from faint to loud, heard at the apex and transmitted into the axilla. This murmur usually increases in intensity after exercise, as do most murmurs heard in children, and is heard best through the diaphragm of a Rieger-Bowles stethoscope with the patient lying on the left side and holding the breath in expiration. This murmur is never transmitted to the neck.[4] It is heard throughout systole up to the second sound, in contrast to most physiologic murmurs. It may sometimes be louder and harsher in late than in early systole. This late, harsh component may sometimes be heard alone and probably indicates a mitral insufficiency which is gradually disappearing.

The quality of this murmur can be appreciated by listening with the bell of the stethoscope on the back of the hand while a finger is passed over the adjacent skin with the lightest possible touch. This description does not include the variations that can occur in the murmur of mitral insufficiency when active carditis is present.

Eighty-seven per cent (1,714) of all children referred for study had a heart murmur. The murmur described in the preceding paragraphs has seemed quite characteristic compared with the murmurs of congenital heart disease and the multitude of rasping, blowing, groaning, rough, harsh, bleating, musical physiologic systolic murmurs that can be heard in the hearts of normal children. The presence of this murmur has been considered sufficient grounds for the diagnosis of rheumatic heart disease with mitral insufficiency, regardless of history or other findings.

All children seen in the diagnostic service were examined by fluoroscopy in the anteroposterior, left anterior oblique and right anterior oblique positions with barium sulfate in the esophagus. Slight localized enlargement of the left ventricle in the anteroposterior position was determined by study of the contour of this chamber in relation to the rest of the heart. If the apex appeared prolonged downward and outward in relation to the rest of the silhouette, enlargement of the left ventricle was considered to be present; if, however, the apex was blunter than usual with broadening of the "waistline," early enlargement of the right ventricle was suspected and confirmation sought in the appearance in the oblique positions.

In the left anterior oblique position, enlargement of the left ventricle was determined primarily by the presence of localized bulging of the lower posterior contour of the heart (although in certain hearts, study of pulsations revealed this to be the left auricle) and only secondarily by whether the heart cleared the spine during quiet respiration. Fulness of the upper posterior border of the heart in this position was considered early enlargement of the left auricle. Bulging of the anterior contour was considered to be enlargement of the right ventricle. In the right anterior oblique position slight indentation of the barium-sulfate-outlined esophagus in the region of the left auricle was observed often in children with normal hearts. Indentation to a degree suggesting enlargement of the left auricle was seldom observed, unless enlargement of this chamber had already been noted in the left anterior oblique position. The pulmonary artery was best observed in a position halfway between the right anterior oblique and the anteroposterior positions. Prominence of this vessel, frequently to a degree

4. This is the observation of Dr. Abe Ravin.

suggesting a small auricular septal defect or a patent ductus arteriosus, was a common finding in children with normal hearts. Localized bulging of the anterior contour in this position was considered enlargement of the right ventricle.

Evaluation of slight degrees of enlargement of the chambers of the heart by fluoroscopy is largely a matter of individual judgment. It can be made more objective, at least in less experienced hands, if the observer always remains in ignorance of the clinical diagnosis and continually makes fluoroscopic studies on children with normal hearts along with those with heart disease. Seventy per cent (1,382) of the 1,971 children examined were judged to have hearts that were normal in size and contour in all positions by fluoroscopy. In actual practice our procedure was to examine by fluoroscope in a group, at the end of each clinic session, all children who had been seen in consultation, without making any

Fluoroscopic Findings in 82 Children with Pure Mitral Insufficiency, 179 Children with Potential Rheumatic Heart Disease and 556 Children with Normal Hearts

	Children with Mitral Insufficiency		Children with Potential Rheumatic Heart Disease		Children with Normal Hearts	
	No.	%	No.	%	No.	%
No. of children	82	100	179	100	556	100
No fluoroscopic findings	39	47.5	145	81	491	88.3
Fluoroscopic findings	43	52.4	34	19	65	11.6
Left ventricle						
Definitely enlarged	20	24.4	3	1.7	1	0.18
Questionably enlarged	9	10.9	19	10.6	33	5.9
Left auricle						
Definitely enlarged	6	7.3	2	1.1	2	3.6
Questionably enlarged	9	10.9	5	2.8	31	5.5
Right ventricle						
Definitely enlarged	2	2.4	1	0.5	1	0.18
Pulmonary artery						
Enlarged or prominent	11	13.4	6	3.4	24	4.3

effort to separate those with normal hearts from those with a clinical diagnosis of heart disease. Against the background of a large number of normal children even minor variations in size and contour were quite noticeable. It is by this method that the presence or absence of enlargement was determined and the criteria of diagnosis evolved as previously outlined.

RESULTS

The results are shown in the table. For comparison, data on 179 children with potential rheumatic heart disease and 556 normal children with no heart disease are also included. This group of 556 was selected to correspond in age and sex with all children seen in this clinic who had either active rheumatic fever or rheumatic heart disease and will be used as a control group in other studies to be reported. Four hundred and twenty-two (76 per cent) of the 556 normal children had a functional systolic murmur: 191 (34 per cent) over the pulmonary area; 131 (23 per cent) over the left sternal border; 6 (1 per cent)

over the aortic area; 21 (4 per cent) between the apex and sternum; 69 (12 per cent) at the apex, and 7 (1 per cent) over the entire heart.[5]

COMMENT

The results of this study indicate that cardiac enlargement visible on fluoroscopy occurs in children with a diagnosis of mitral insufficiency based on the presence of a characteristic murmur, but that such enlargement is by no means the rule.

Twenty-four per cent of the 82 children with mitral insufficiency showed enlargement of the left ventricle, compared with 1.6 per cent of those with potential rheumatic heart disease. The finding of 1 child with enlargement of the left ventricle, 2 with enlargement of the left auricle and 1 with enlargement of the right ventricle in a group of 556 children with otherwise entirely normal hearts was probably simply an error in judgment.

Seham, Shapiro and Hilbert [2c] reported 42 per cent of their children with mitral insufficiency to have roentgenologic abnormalities at the time of the first visit. Wilson [6] observed that when children with mitral insufficiency were studied fluoroscopically in the left anterior oblique position, 84 per cent of them had an angle of clearance greater than 55 degrees. In Kuttner and Markowitz's series of 144 cases,[2b] 83 children had no cardiac enlargement by roentgenogram and the hearts of the remaining 61 showed no clinical enlargement. Clinical evaluation of slight degrees of enlargement has proved worthless in our hands because 5 of the 39 hearts with no fluoroscopic abnormalities were thought to be enlarged clinically, while only 6 of 20 with enlargement of the left ventricle visible on fluoroscopy were thought to have clinical enlargement.

Another approach to this problem has been made by Boone and Levine [2d] and Kuttner and Markowitz.[2b] Boone and Levine compared a group of 59 children who had the murmur of mitral insufficiency with a group of 166 children classified as having potential rheumatic heart disease and discovered that in 42 per cent of the former group the murmurs of mitral stenosis and aortic insufficiency appeared in 9.6 years, while in only 4.8 per cent of the latter group did further evidence of cardiac damage develop. Kuttner and Markowitz made a similar comparison between 144 children with mitral insufficiency and 171 children with potential rheumatic heart disease. They found that 48 per cent of the former and 13 per cent of the latter showed further evidence of organic heart disease after a follow-up period of slightly more than

5. Small discrepancies in totals are due to an occasional error, either in the coding of the charts or the punching of the cards.

6. Wilson, M. G.: Clinical Radioscopic Studies of the Heart in Children. Am. J. Dis. Child. **47**:750 (April) 1934.

eight years. Both investigators concluded that mitral insufficiency could be diagnosed in the presence of a characteristic murmur and in the absence of cardiac enlargement, because children with such a murmur showed further signs of valvular damage so much oftener than children with "potential rheumatic heart disease." In our experience this murmur need not be as loud as described by Kuttner and Markowitz; its intensity may be as faint as that of the diastolic murmur of early aortic insufficiency.

If it is correct that mitral insufficiency can exist in the absence of cardiac enlargement, it seems important that the fact be recognized because this group with early rheumatic heart disease stands to benefit most by measures designed to prevent rheumatic recurrences.

SUMMARY

The records of 1,971 children seen during the first two years of operation of the Denver Area Rheumatic Fever Diagnostic Service were examined to determine whether cardiac enlargement is necessarily present in mitral insufficiency, diagnosed on the basis of the presence of a characteristic murmur.

There were 82 children with a diagnosis of mitral insufficiency. Of these, 20 (24 per cent) showed enlargement of the left ventricle when examined by fluoroscopy in the anteroposterior and left anterior oblique positions. For controls, there were included 179 children with potential rheumatic heart disease. Three (1.6 per cent) of these showed enlargement of the left ventricle. One of the 556 children with clinically normal hearts showed enlargement of the left ventricle.

These observations support the conclusions that the diagnosis of mitral insufficiency can be made in the presence of the characteristic murmur and that cardiac enlargement need not necessarily be present.

The statistical division, the Bureau of Maternal and Child Welfare, District of Columbia Health Department, Washington, D. C., assisted in the preparation of this paper. Friends of the Rheumatic Fever Diagnostic Service helped with the coding of these records.

Children's Hospital (Dr. Wedum).

EPIDERMOLYSIS BULLOSA

A. MATHESON, M.D.
AND
DAVID C. ROSNER, M.D.
CHICAGO

THE INFREQUENCY of epidermolysis bullosa in pediatric practice, its occurrence in four members of a family and its presence at birth in a premature infant prompt us to present a paper on this subject. This is a disease of the skin or associated structures, probably of hereditary origin, characterized by the development of vesicles and bullae on a minimum of trauma. The condition was first described by von Hebra in 1870, but not until 1886 was the name "epidermolysis bullosa" given. A number of classifications has been set forth in the literature, but three essential types, as listed by Cockayne,[1] are most commonly referred to: (1) epidermolysis bullosa simplex (2) epidermolysis bullosa dystrophica, dominant form, and (3) epidermolysis bullosa dystrophica, recessive form.

Epidermolysis bullosa simplex is usually first noted in infancy, with the bullae located on the areas exposed to injury or friction. The degree of trauma that will result in lesions is variable. The bullae are formed in the horny layer [2] or in the prickle cell layer [3] of the epidermis. The lesions on healing leave no scars except on exposed parts of the body where trauma is frequent, such as the tips of the fingers. The hair, teeth, mucous membrane and nails are normal. The formation of bullae may cease at a later age, usually at puberty. Although the disease may persist throughout life, the general health of the patient is unaffected. Hyperhidrosis of the palms and soles is frequently observed, associated with the cutaneous lesions. The simplex type is strongly hereditary.[4]

Read before the Chicago Pediatric Society, Jan. 18, 1949.

From the Sarah Morris Division of the Michael Reese Hospital.

1. Cockayne, E. A.: Inherited Abnormalities of the Skin, London, Oxford University Press, 1933.

2. Elliot, G. T.: Two Cases of Epidermolysis Bullosa, J. Cutan. & Genito-Urin. Dis. **13**:10, 1895.

3. Török, L.: Epidermolysis Hereditaria Bullosa (Koebner), Arch. f. Dermat. u. Syph. **47**:402, 1899.

4. Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, ed. 10, St. Louis, C. V. Mosby Company, 1939, p. 562.

Epidermolysis bullosa dystrophica, dominant form, is intermediate in severity between the simple form and the recessive dystrophic form. The bullae are located between the epidermis and the corium.[5] The mucous membranes are usually involved, though not so frequently as in the recessive form. The teeth and hair are normal, but the nails are frequently thickened and clawlike. The bullae on healing leave thin atrophic scars, with epidermal cysts commonly seen about the scars singly or in groups. Dermographia is sometimes seen. Hyperhidrosis of the palms and soles is common.

Epidermolyis bullosa dystrophica, recessive form, is present at birth or appears soon after. As in the dominant form, the bullae are located between the epidermis and corium. Miminal trauma provokes lesions; they are also frequently present on the mucosal and conjunctival areas. The bullae have been observed on the nose, lips, mouth, tongue, pharynx, larynx and, occasionally, the esophagus and bronchi. Corneal opacities may result following the lesions on the conjuntiva and cornea. The nails are deformed and the teeth, which are abnormal, decay rapidly. Hyperhidrosis of the palms and soles is a prominent feature. Many of the patients are small in stature and have less than normal intelligence.

Karelitz,[6] Wise and Lautman,[7] Fox,[8] Hallam[9] and MacKee and Cipollaro[10] in various reports have attempted to separate cases of epidermolysis bullosa into congenital and acquired forms. The difference between the two forms is that the onset in the acquired type is considered to occur after the third year of life. The clinical picture of both types being the same, such a division is hardly justified. However, there may be some basis for differentiation of another type, Heinrichsbauer's[11] type, or "epidermolysis bullosa hereditaria letalis,"[12]

5. Engman, M. F., and Mook, W. H.: A Study of Some Cases of Epidermolysis Bullosa, with Remarks upon the Congenital Absence of Elastic Tissue, J. Cutan. Dis. **24**:55, 1906; A Further Contribution to the Study of Elastic Tissue in Epidermolysis Bullosa, ibid. **28**:275, 1910.

6. Karelitz, R.: Ein Beitrag zur Frage der Epidermolysis bullosa (hereditaria et acquisita), Inaug. Dissert., Rostock, 1904; cited by Wise and Lautman.[7]

7. Wise, F., and Lautman, M. F.: Epidermolysis Bullosa Beginning in Adult Life: The Acquired Form of the Disease, J. Cutan. Dis. **33**:441, 1915.

8. Fox, H.: Epidermolysis Bullosa, Acquired, J. Cutan. Dis. **33**:148, 1915.

9. Hallam, R., in Rolleston, H.: The British Encyclopedia of Medical Practice, London, Butterworth & Co., Ltd., 1937, vol. 5, p. 82.

10. MacKee, G. M., and Cipollaro, A. C.: Skin Diseases in Children, New York, Paul B. Hoeber, Inc., 1936, p. 197.

11. Heinrichsbauer, F.: Ein weiterer Beitrag zur Frage angeborener Hautdefekte, Arch. f. Gynäk. **134**:673, 1928.

12. Herlitz, G.: Kongenitaler, nicht syphilitischer Pemphigus: Eine Uebersicht nebst Beschreibung einer neuen Krankheitsform (Epidermolysis bullosa hereditaria letalis), Acta pædiat. **17**:315, 1935.

when death occurs before the third month of life. It is questionable whether such nomenclature is advisable as this term implies death due to the cutaneous lesions directly, whereas in a number of instances death could easily be explained as due to secondary infection of the cutaneous lesions followed by sepsis.

A few cases [13] have been reported in the literature as epidermolysis bullosa hereditaria,[14] the features associated with the hereditary aspect of the disease being as follows: Epidermolysis bullosa simplex is considered to be an irregular dominant, since it behaves as a regular dominant in some families, while in others it may skip a generation with the defect being transmitted by an apparently normal person. In none of the families with the simple form has any one person had lesions of the dystrophic form, though both forms are inherited. In the families studied, it has been shown that in the full sibships the proportion of affected to normal sibs is 201 : 163, thus indicating that the disease is a dominant. This is correlated with the fact that the ratio of an expected dominant is 1 : 1. Among those who are affected, the proportion of males to females is 150 : 100. Consanguinity of parents is found frequently. In one series of 23 cases of epidermolysis bullosa dystrophica, 14 included a history of parental consanguinity.[1]

PATHOGENETIC ASPECTS

The essential changes present in most cases are: (1) loosening or separation of epidermis from underlying tissues, (2) decrease of elastic tissue in skin, (3) presence of the Nikolsky sign (the outer layer of skin is rubbed off by slight trauma) and (4) little or no inflammatory change. Engmann and Mook [5] observed the elastic tissue of the papillary and subpapillary regions to be absent and deformed in the deeper layers of the skin. However, many cases of epidermolysis bullosa failed to demonstrate the lack [1] or depletion of the elastic tissue.[15]

There are two essential theories to explain the pathologic changes. The vascular theory states that a hereditary abnormality exists in the vascular system of the skin with the result that the basal portion is bathed in a serous transudate; this causes degenerative changes in the elastic tissue with the separation of the skin. The second theory assumes that the defect is in the elastic tissue primarily. The fact that dermographia frequently occurs in both the simple and the dystrophic forms indicates the presence of vascular abnormality. However, no

13. Luithlen, F.: Epidermolysis Bullosa Hereditaria, in Mraček, F.: Handbuch der Hautkrankheiten, Vienna, A. Hölder, 1902, vol. 1, p. 738.

14. Davidson, L. T.: Hereditary Epidermolysis Bullosa: Report of Case with Résumé of Literature, Am. J. Dis. Child. **59**:371 (Feb.) 1940.

15. Craig, H. R.: Epidermolysis Bullosa, Am. J. Dis. Child. **39**:898 (April) 1930.

pathologic changes have been observed in the vessels. It is possible that there is an abnormal vasomotor nervous control or cellular damage caused by a circulating toxin.[16]

There has been an attempt to correlate the similarity of epidermolysis bullosa to congenital porphyria, since slight trauma causes the formation of bullae in both diseases. Structural anomalies, such as deficiency of elastic tissue, are also common to both diseases. As many as 15 cases of epidermolysis bullosa with porphyria have been reported.[17] Sunlight, however, plays no part in epidermolysis bullosa, while in porphyria it is an important factor in the formation of bullae.

REPORT OF CASES

CASE 1.—B. S., a white girl delivered spontaneously with cephalic presentation on Aug. 23, 1947, was brought to Sarah Morris Hospital on the day after birth. The weight at birth was 3 pounds 8 ounces (1,588 Gm.). The mother

Fig. 1 (case 1).—Photograph of B. S., a premature infant, demonstrating the absence of epithelium over the extensor surfaces of the elbows, knees and ankles. Lesions are also seen over the nose and on the upper part of the abdomen.

had had an uneventful pregnancy and a negative blood Kahn reaction. The calculated fetal age at birth was 34 weeks. The physical examination of the newborn child revealed an absence of epithelium over the extensor surfaces of the elbows, knees and ankles (fig. 1). In place of the epithelium there was a dark brownish transparent membrane which was smooth and continued into apparently normal skin. Through these denuded areas one could easily visualize the deeper structures—the blood vessels, nerves, tendons and muscles. Denuded areas were also present over the left side of the nose, extending for 1 cm. over the adjacent area, at the umbilicus and on the soles. These areas showed no evidence of erythema or suppuration.

16. Elliot, G. T.: A Further Contribution to the Histopathology of Epidermolysis Bullosa (Hereditaria), New York M. J. **71**:585 and 625, 1900.

17. Kierland, R. R., and Harrison, M. W.: Epidermolysis Bullosa with Unusual Distribution and Elevated Urinary Porphyrins, Proc. Staff Meet., Mayo Clin. **15**:313, 1940.

The infant was fed breast milk by dropper after twenty-four hours of starvation. She was given penicillin therapy prophylactically and was put in an incubator bed with an oxygen inhalator. Emesis occurred twice, on August 24 and 25, twenty-four hours after her admission to the hospital. On August 26 no notable changes were seen in the cutaneous lesions, with the exception of formation of bullae on the lumbar area. On that date jaundice was first noted and the infant was unable to take feedings. The jaundice deepened, sternal retractions were present, and the infant died that evening. The baby had been afebrile throughout her stay in the hospital.

The Wassermann and Kahn reactions had been negative on August 24. Roentgenograms of the entire skeleton had revealed no skeletal anomalies or pathologic change. No history was obtained of similar cutaneous lesions in members of the family.

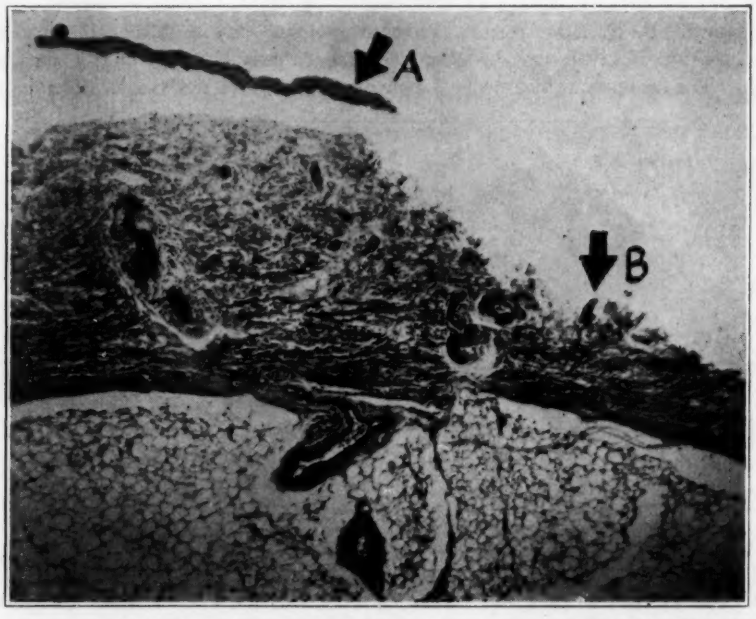

Fig. 2 (case 1).—Section through the skin. Note the lack of inflammatory cells. *A* is the thin and flat epidermis which is separated from the dermis. *B* indicates the absence of epidermis and hyperkeratosis of the dermis. Hematoxylin and eosin stain.

Postmortem Examination.—On external examination the skin everywhere, including the scalp, peeled off on touch and left a smooth shining surface exposed. Of microscopic sections through the skin where the epidermis was missing, the following description was given by the pathologist:

"The surface of the corium was dark red to blue and the nuclei throughout the corium were pyknotic. There was little, if any, inflammatory reaction. Where the epidermis was present, the rete pegs were small and widely spaced. The epidermis appeared thin and flat. In areas adjacent to the epidermal defect the stratum corneum was elevated and separated from its subjacent tissue. The entire thickness of the epidermis was lacking in the denuded areas, the exposed surface of which consisted of peripheral dermis. Elastic tissue was sparse and apparently fragmented (fig. 2), but comparable in amount to that of an infant of similar gestation."

Thus, the condition may be classified as epidermolysis bullosa, simplex type.

In the kidneys on gross examination, there were triangular areas of orange streaks in the pyramids. Orange crystals were also seen in the ureters, and there was a deposition of bright material at the trigone of the urinary bladder. On microscopic section, the pathologist reported, "the tubules at the papillary tips were extremely dilated and contained refractile eosinophilic material. This on close examination appeared to be made up of small circular or globular forms. Mixed with this were many desquamated cells. The tubular epithelium of the convoluted tubules showed much swelling and granularity. The prussian blue reaction for iron in the tubular casts was negative." Study of the urinary substance for fluorescence under ultraviolet rays was done, but specimens did not show the presence of porphyrins.

The lungs showed evidence of pneumonic consolidation; this was especially noted in the lower lobes of both lungs. The tracheobronchial tree was plugged

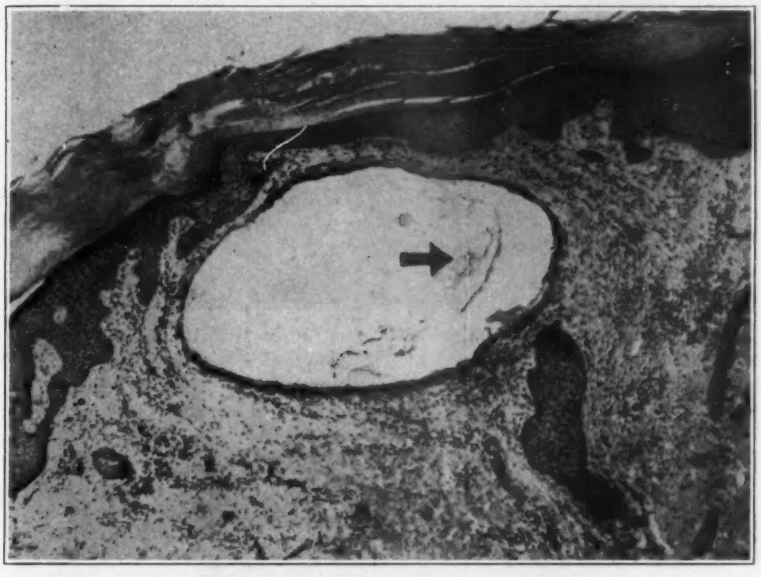

Fig. 3 (case 2).—Section of the skin with a bullous lesion (arrow) in the subpapillary layer of the dermis. Hematoxylin and eosin stain.

with greenish yellow, thick mucoid material. The liver and spleen were normal. Bloody fluid was around the brain with clotted blood at the base and in the lateral ventricles.

Case 2.—J. D. S., a 5 year old girl, was admitted to Sarah Morris Hospital on April 3, 1948 because of a mass the size of a hen's egg in the inguinal region. This proved to be a tuberculous lymph gland. An incidental observation was cutaneous lesions on both knees and elbows, present almost constantly since the age of 1 year, which may be described as follows: On the anterior surfaces of both knees and elbows, as well as on the lateral aspects of the ankles, there were reddish brown patches of dry, wrinkled skin which was thinner than the surrounding skin and had a dark brown periphery. Set in these patches were firm cutaneous nodules which were shiny pink and seemed to be made up of multiple milia. These milia were of pinhead size and hard. The patches about the left ankle showed recent blister sites.

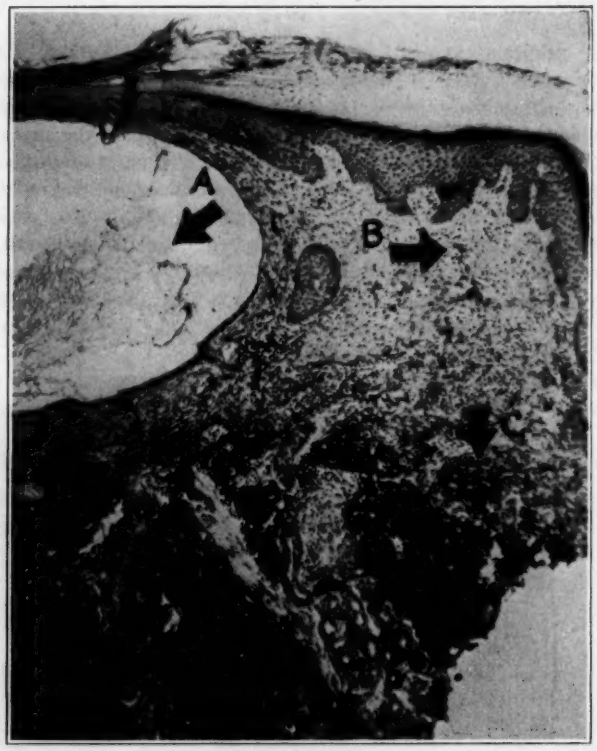

Fig. 4 (case 2).—Section of the skin. *A* is the bulla in the subpapillary region. *B* reveals a pronounced decrease of elastic tissue and the absence of inflammatory cells. *C* indicates fragmentation of the elastic tissue. Orcein stain.

Fig. 5 (case 4).—Photograph showing hemorrhagic bullous lesion on the inferior surface of the knee and another bulla on the middle volar portion of the leg.

A biopsy specimen from the blister sites revealed slight hyperkeratosis on microscopic examination. There was a small vesicle present in the upper layer of the dermis, just beneath the epidermis (fig. 3). Within the dermis were small accumulations of lymphocytes localized about the hair shafts and small blood vessels. There was a pronounced sparsity of elastic fibers in the dermis (fig. 4).

CASES 3 and 4 (the patients were the brother and mother of the patient of case 2).—The 7 year old brother had lesions on the arms, hands, fingers and legs, similar to those of the preceding patient (case 2). The slightest trauma produced vesiculation, followed by crusting and secondary infection, thus incapacitating the child. Similarly, the mother had had lesions since early childhood on the extensor surfaces of the arms and legs, with formations of large bullae which were hemorrhagic at times (fig. 5). These would rupture and become secondarily infected so that she was forced to wear bandages about the lesions on the arms and legs almost constantly. The maternal grandmother had similar lesions but would not allow us to take photographs.

COMMENT

We have shown, then, examples of two types of epidermolysis bullosa. The first was the acute type and the second the chronic, disabling type. The death of the first patient was due to bronchopneumonia. The cutaneous defect involving many exposed surfaces of the body in this patient is, to our knowledge, the first recorded in a premature infant with presumptive evidence of the lesions having been present in utero. Urinary porphyrins were not demonstrated. Laboratory data, such as blood nonprotein nitrogen, urea nitrogen, creatinine, chloride and vitamin A and C levels, are within normal limits in this disease. One report [18] revealed the blood cholesterol to be below normal during a remission stage and elevated during exacerbation. Porphyrinuria is not usually present. Culture of the fluid from the bullous lesions is usually sterile unless secondary infection occurs. One isolated report of 3 cases by Cannon, Sanders and Rankin [19] demonstrated an unusual type of hemolytic streptococcus (group G, Lancefield) in the bullae but it is questionable whether the organism was the etiologic agent.

In the differential diagnosis of the cutaneous lesions at, or soon after, birth one must include congenital syphilis, pemphigus neonatorum, exfoliative dermatitis (Ritter's disease), congenital cutaneous defects and chickenpox or smallpox in the newborn. In syphilis the lesions are less frequently seen on the face and extensor surfaces of the upper and lower extremities but more on the back, buttocks, posterior part of the thighs and palms and soles. Roentgenologic studies of bones and serologic reactions may be important when positive findings are present.

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18. Mortimer, E. N.: Epidermolysis Bullosa Hereditaria, J. Pediat. **28**:613, 1946.

19. Cannon, A. B.; Sanders, M., and Rankin, J. L., Jr.: Epidermolysis Bullosa: A Clinical and Bacteriologic Study, Arch. Dermat. & Syph. **42**:884 (Nov.) 1940.

In pemphigus neonatorum lesions begin as erythematous macules which coalesce and form pustules by the third or fourth day of life. In addition, streptococci or staphylococci may be obtained from the unruptured vesicles. In exfoliative dermatitis bullae are present only rarely. In chickenpox and smallpox the disease is either present or recent in the mother. In congenital cutaneous defects no bullae appear and the Nikolsky sign (slight trauma can remove outer layer of skin) is not elicited. It is possible that some of the conditions described in the literature as congenital cutaneous defects are in reality epidermolysis bullosa.

There is no specific treatment for this condition of the skin, except the treatment of secondary infection when it occurs. Sulfanilamide has been administered in some instances with reported benefit. Kittredge [20] reported definite improvement in a case by the use of iron cacodylate, calcium, phosphorus and roentgen rays.

SUMMARY

The etiologic and pathogenetic aspects of epidermolysis bullosa are briefly reviewed. Four case histories, including photographs and results of biopsies of the skin, are presented. The first case is that of a premature infant, 1 day old, who was admitted to the hospital because of large denuded areas of skin on the thighs and lower arms. The other cases are of 2 children, 5 and 7 years old respectively, and their mother. All had cutaneous lesions on the extremities from infancy. The lesions were chronic, recurrent and productive of bullae on slightest trauma. The mother was incapacitated because of almost constant lesions on the fingers of both hands. The characteristic microscopic changes in all instances were: (1) absence or separation of epidermis from subjacent tissue, (2) sparsity of elastic tissue in the superficial layers of the skin and (3) absence of inflammatory change.

Such lesions in the newborn have to be differentiated from those of congenital syphilis, pemphigus neonatorum, congenital cutaneous defects and chickenpox. Differential points are presented. The hereditary aspect of the disease is stressed. There is no specific treatment for this cutaneous disease.

30 North Michigan Avenue.

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AGGLUTINATING SUBSTANCES FOR HOMOLOGOUS COLIFORM ORGANISMS

Observations on Their Occurrence in the Serum and Feces of Infants

EDWARD F. RABE, M.D.
AND
DONAL L. DUNPHY, M.D.
With the Technical Assistance of Mildred D. Fousek and Polly A. Peck
NEW HAVEN, CONN.

THE PATHOGENICITY of coliform organisms is most commonly recognizable in infections of the urinary tract. Siede and Luz [1] observed that 80 per cent of 63 patients with disease of this nature exhibited elevated serum agglutinins ($> 1:80$) for homologous strains of coliform bacilli nine days or more after the onset of illness. Although the possibility has been suggested that coliform organisms might similarly be concerned in the pathogenesis of infantile diarrhea, no conclusive evidence on the subject has appeared. Ruchman and Dodd [2] recently observed that during the course of illness there occurred a rise in titer of serum agglutinins for a homologous coliform organism isolated from a patient with infantile diarrhea.

The occurrence of agglutinating substances for dysentery bacilli in the feces of patients with dysentery was noted by several investigators.[3] Harrison and Banvard [3a] observed that the fecal agglutinin titer rose rapidly in such patients during the acute stage of diarrhea and fell during convalescence. This was accompanied with a slow rise in the titer of serum agglutinins during the acute stage of the disease, with a sustained high level being demonstrable during convalescence.

Aided by a grant from the James Hudson Brown Memorial Fund of the Yale University School of Medicine.

From the Department of Pediatrics, Yale University School of Medicine, and the University Service, Grace-New Haven Community Hospital.

1. Siede, W., and Luz, K.: Agglutinabilität und Pathogenität des Bact. coli bei Erkrankungen der Harnwege, Klin. Wchnschr. **10**:241, 1941.

2. Ruchman, I., and Dodd, K.: The Isolation of a Strain of E. Coli Pathogenic for the Rabbit's Eye from a Patient with Diarrhea, J. Bact. **53**:653, 1947.

3. (*a*) Harrison, P. E., and Banvard, J.: Coproantibody Excretion During Enteric Infections, Science **106**:188, 1947. (*b*) Davies, A.: An Investigation into the Serological Properties of Dysentery Stools, Lancet **2**:1009, 1922. (*c*) Prodtchensky, S., and Moroz, O.: A Method for Early and Rapid Diagnosis of Dysentery, Zhur. Mikrobiol., Epidemiol., Immunol., Moscow **7**:3, 1940.

The investigations of Burrows and Havens[4] on fecal agglutinins in guinea pigs and human beings indicated that these substances are globulins which are indistinguishable in antigenicity and antibody activity from homologous immune serum globulins.

The capacity of babies in the neonatal period and of infants to produce antibodies was demonstrated,[5] although, in general, antibody production at this age has been thought to be quantitatively small and qualitatively different from that of adults. Recent experience with immunizations in newborn infants lent support to this earlier impression.[6] It is also known that newborn infants receive agglutinins for coliform organisms transplacentally,[7] but it has been assumed that these substances are quickly lost.

In view of these observations, it seemed worth while to carry out investigations in an attempt to answer the following questions. Do substances capable of agglutinating coliform organisms obtained from the infants' own intestinal tract occur in the serum and feces of babies? If these substances are present, is there a difference in incidence and titer of these substances between healthy babies and babies with diarrhea of unknown origin? Can the occurrence and titer of these substances be correlated with the clinical course of infantile diarrhea? It was thought that answers to these questions might yield information about the possible relation between coliform organisms and diarrhea in infants.

MATERIAL AND METHODS

All the patients included in this study were hospitalized in the pediatric service of the Grace-New Haven Community Hospital. Samples of blood and feces were obtained from each patient on the same day whenever possible. Samples of serum and feces collected from the patient on the same day are hereafter referred to as "parallel" specimens.

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4. Burrows, W., and Havens, I.: Studies on Immunity to Asiatic Cholera: V. The Absorption of Immune Globulin from the Bowel and Its Excretion in the Urine and Feces of Experimental Animals and Human Volunteers, J. Infect. Dis. **82**:231, 1948.

5. (*a*) Baumgartner, L.: The Relationship of Age to Immunological Reactions, Yale J. Biol. & Med. **6**:403, 1934. (*b*) McKahn, C. F., and Kapnick, I.: Immunity and Susceptibility to Disease in Early Infancy, J. Pediat. **13**:907, 1938. (*c*) Burnet, F. M.; Frieman, M.; Jackson, A. V., and Lush, D.: The Production of Antibodies, Monograph No. 1, Walter and Eliza Hall Institute of Research in Pathology and Medicine, London, The Macmillan Company, 1941, chap. 8.

6. di Sant'Agnese, P. A.: Combined Immunization Against Diphtheria, Tetanus, and Pertussis in Newborn Infants: III. Relationship of Age to Antibody Production, Pediatrics **3**:333, 1949.

7. Toomey, J. A.: Agglutinins in Mother's Blood, Baby's Blood, Mother's Milk and Placental Blood, Am. J. Dis. Child. **47**:521 (March) 1934.

Three groups of patients were studied. In the control group, numbering 17 babies 1 day to 7 months of age, none had diarrhea either during or preceding the period of collection of blood and stool samples. From 11 babies 6 days to 7 months of age parallel samples of serum and stool were collected once for titration against homologous strains of coliform organisms. From the remaining 6 patients, which included 3 newborn babies and 3 infants 3, 4 and 6 months of age, parallel samples were collected on three or four occasions over a period of ten to fourteen days.

The second group of patients included 12 babies with epidemic diarrhea of the newborn. They ranged in age from 4 to 21 days. Seven of the babies came from hospital nursery A and 3 from hospital nursery B; they represented respectively two separate outbreaks of diarrhea which occurred during January and February 1948. The remaining 2 babies were admitted from two other hospitals. Multiple and parallel samples of serum and feces were obtained from each of the babies over periods of observation ranging from seven to twenty-nine days, which included the second to thirty-seventh days of illness. However, not all these samples of serum and feces were parallel. Fecal samples were obtained from all patients during the acute and convalescent stages of the disease. Acute and convalescent serums were obtained from 9 of the 12 babies studied.

The third group of 8 patients was composed of those with sporadic acute diarrhea admitted to the hospital from December 1947 to June 1948. The babies ranged in age from 5 weeks to 11½ months. Multiple parallel specimens of blood and feces were obtained from these patients over a period of nine to fifty-eight days, representing the second to one hundred and twenty-fourth days of illness.

Blood for culture was routinely obtained from all patients on their admission to the hospital. Cultures were made by inoculating 5 cc. of patient's blood into 50 cc. of broth and by mixing 2 cc. of patient's citrated blood with 15 cc. of infusion agar to form a pour plate. None of the patients was demonstrated to have a bacteremia. Blood for agglutination studies was collected, and the serum was stored in sterile containers at ice box temperature without an added preservative. Serial samples were drawn at five to ten day intervals.

Stools were collected from diapers. Occasionally, tubes were attached to male babies and they were placed on collecting containers to facilitate the separate collection of feces and urine. Serial samples of feces were taken at two to five day intervals. Stool specimens were weighed and sufficient isotonic sodium chloride solution was added to make a dilution of 1:7.5 by weight. The suspension was agitated vigorously for ten minutes, then centrifuged an hour at 3,200 revolutions per minute. Filtration through no. 615 paper and recentrifugation were occasionally needed to obtain a clear but colored solution. The resulting supernate, with 0.5 per cent solution of formaldehyde U. S. P. added, was stored in sterile tubes at approximately 4 C. (39 F.). Agglutinin titers were determined within three weeks of collection; during this period titers were found to be reproducible.

Specimens of stool were obtained on a dry cotton swab from the rectum of each patient. The material was cultured on Endo's medium and shigella-salmonella thiosulfate-citrate bile agar plates. Cultures were obtained from each patient on admission and were repeated during the next three days. In the study of newborn infants, cultures were obtained only on the fifth day of life. One coliform colony was picked from each of the two plates used. A pure culture of each lactose-positive colony so picked was then classified according to the well known

indole, methyl red, Voges-Proskauer and citrate reactions. Motility was not routinely determined. Slow lactose or nonlactose fermenters were thoroughly investigated for purposes of classification. Several strains of the following enteric organisms were isolated from patients during the study; Escherichia coli, Aerobacter aerogenes, coli aerogenes intermediate, Proteus mirabilis [8] and Proteus morganii. A strain of paracolon bacillus was isolated from a patient on one occasion. No shigellae or salmonellae organisms were encountered.

Two strains of coliform organisms isolated from each patient were used in the agglutinin determination. Two types of antigens were prepared from each strain, a K antigen and an O^{121} antigen. These antigens appear to correspond with the "capsular" and somatic antigens of Kauffmann.[9] The K antigen was prepared from an eighteen to twenty-four hour growth on thick agar plates enriched with a 0.2 per cent glucose solution. The organisms were washed off with 5 cc. of isotonic sodium chloride solution, and the bacterial suspension was stored at 4 C. for a maximum of two weeks. For use in agglutination tests a portion of the suspension was further diluted with isotonic sodium chloride solution to correspond to the density of MacFarlane nephelometer tube no. 4 prior to each titration. The O^{121} antigen was prepared by growing the organism for eighteen to twenty hours in broth. The organisms were sedimented by centrifugation and then were suspended in saline solution; the suspension was autoclaved for two hours at 121 C. (250 F.). After cooling, solution of formaldehyde U. S. P. (0.5 per cent) was added as a preservative and the suspension was stored at 4 C. for two weeks. Prior to use a portion of the suspension was diluted to a density corresponding to MacFarlane nephelometer tube no. 4.

Titrations of serum and fecal suspensions were performed with 0.2 cc. aliquots of antigen and agglutinin. Serial twofold dilutions of unheated serum from 1:10 to 1:2,560, plus a saline control, and serial twofold dilutions of fecal suspension from 1:7.5 to 1:1,920, plus a saline control, were used. A standard coliform antigen and a homologous rabbit antiserum were periodically run as a control of the method. Mixtures of antigen and serum or fecal suspension using the viable K antigen were incubated for two hours in a 37 C. (98.6 F.) water bath. Similar mixtures using the inactivated O^{121} antigen were incubated two hours at 56 C. (133 F). After the specimens stood overnight at 4 C. readings were made with an angled mirror and constant light source by noting the dispersion pattern of bacteria on the bottom of the tube. The agglutination observed was graded from 0 to 4 plus. Titers were expressed as the final dilutions of serum or feces which produced a 2 plus agglutination of the antigen.

RESULTS

The O^{121} antigen and the K antigen were employed in the study of 6 patients in the control group and 5 patients in the group with sporadic diarrhea. Serum and fecal suspensions were tested with both antigens, which were prepared from homologous strains of coliform organisms. The O^{121} antigen was not used further because of incon-

8. Proteus mirabilis is nonspreading and gives negative reactions to indole and maltose.

9. Kauffmann, F.: The Serology of the Coli Group: Review, J. Immunol. **57**:71, 1947.

sistencies which were repeatedly observed. These inconsistencies were: (*a*) the O^{121} antigen often exhibited spontaneous agglutination in isotonic sodium chloride solution, whereas the corresponding K antigen did not; (*b*) fecal suspensions (but not serum) occasionally caused lysis of the O^{121} antigen in appreciable dilution but did not lyse the K antigen; (*c*) the O^{121} antigen of seven strains did not agglutinate with serum or fecal suspensions, whereas the K antigen of the same strain agglutinated to titers up to 1:320. The data presented in the tables and charts are, therefore, the results of titrations of serum and fecal suspensions against the K antigen prepared from two strains of homologous coliform organisms obtained from each patient.

Table 1 summarizes data relative to the question of whether or not substances occur in the serum or feces of babies which are capable of agglutinating gram-negative organisms obtained from the infants' own intestinal tracts. It can be calculated from this table that agglu-

TABLE 1.—*Incidence of Serum and Fecal Agglutinins for K Antigen of Homologous Coliform Organisms*

Group	No.	Serum Agglutinins		Fecal Agglutinins	
		% Patients with Titers		% Patients with Titers	
		≥1:20	>1:80	≥1:15	>1:60
Controls, <1 mo.	6	83.3	0	0	0
Controls, >1 mo.	11	72.7	27.2	27.2	0
Infants with epidemic diarrhea	12	83.3	25.0	75.0	41.6
Infants with sporadic diarrhea	8	75.0	50.0	75.0	37.6

tinating substances for homologous coliform organisms occurred in the serum of 13 (76.4 per cent) of 17 well babies and in 16 (80 per cent) of 20 babies ill with diarrhea. On the other hand, agglutinating substances for homologous coliform organisms occurred in the feces of 3 (17.6 per cent) of 17 well babies but in 15 (75 per cent) of 20 babies ill with diarrhea of unknown origin.

In charts 1 and 2 the distribution of the titers of each sample of serum and feces is shown. The serum agglutination titers for the control group ranged from 0 to 1:1,280, the higher titers occurring in the older babies. In babies with diarrhea the serum agglutination titers ranged from 0 to 1:2,560, and again the higher titers occurred in older patients. The titers of agglutinating substances in the feces ranged from 0 to 1:60 in the control patients and from 0 to 1:960 in the babies with diarrhea. The factor of age did not appear to influence the titer of fecal agglutinating substances.

The data presented in table 1 were analyzed statistically to determine whether or not there existed a significant difference in incidence and titer of serum and fecal agglutinating substances between normal babies

PATIENT'S AGE (MONTHS)		SERUM AGGLUTINATION TITER									
		0	1/20	1/40	1/80	1/160	1/320	1/640	1/1280	1/2560	1/5120
CONTROLS	0-1	•••	••	•••	•						
	1-3	••••				•					
	3-6	•••	••	•				•			
	6-12	••	•						•		
DIARRHEA	0-1	ooooo	oo	ooooo	ooooo oo	ooooo	oo				
	1-3	+++++ +++++ +++++	++	+++++			+	++++			
	3-6		++	+	+	+++	++++	++	+		
	6-12								+	++	

Chart 1.—Serum agglutination titers for K antigen of homologous coliform organisms. There were 17 controls (represented by dots) from whom 25 samples were obtained, 12 patients with epidemic diarrhea (represented by circles) from whom 26 samples were obtained and 8 patients with sporadic diarrhea (represented by crosses) from whom 44 samples were obtained. Each dot, circle or cross represents one sample.

PATIENT'S AGE (MONTHS)		FECAL AGGLUTINATION TITER									
		0	1/15	1/30	1/60	1/120	1/240	1/480	1/960	1/1920	1/3840
CONTROLS	0-1	••••• ••••• •									
	1-3	•••		•	•						
	3-6	••••• •••		•							
	6-12	•••••									
DIARRHEA	0-1	ooooo ooooo ooooo ooooo	oooo	ooooo	ooooo o	o	ooo	o	o		
	1-3	+++++ +++++ +++++ +++++	+++	+	++						
	3-6	+++++	+++	++	++						
	6-12	+				+	+		+		

Chart 2.—Fecal agglutination titers for K antigen of homologous coliform organisms. There were 17 controls (represented by dots) from whom 30 samples were obtained, 12 patients with epidemic diarrhea (represented by circles) from whom 42 samples were obtained and 8 patients with sporadic diarrhea (represented by crosses) from whom 56 samples were obtained. Each dot, circle or cross represents one sample.

and babies with diarrhea of unknown origin. The results of this analysis are summarized in table 2. The occurrence of agglutinating substances for homologous coliform organisms in the serums of babies with epidemic diarrhea of the newborn or with sporadic diarrhea did not differ significantly from the occurrence of these substances in well babies of comparable age. The appearance of elevated serum titers ($>1:80$) was also not significantly different in the two groups of babies with diarrhea when compared with the control group.

Fecal agglutinins, however, were not demonstrated in any of the well babies under 1 month of age, but these agglutinins were observed in 8 (75 per cent) of 12 babies with epidemic diarrhea of the newborn. This greater incidence of fecal agglutinins in babies with epidemic diarrhea of the newborn than in control subjects of the same age is, statistically, highly significant. Among infants 1 to 11 months of age fecal agglutinins were noted in 3 (27.2 per cent) of 11 well patients but in 6 (75 per cent) of 8 babies ill with diarrhea of unknown origin.

TABLE 2.—*Summary of Calculations of Statistical Significance; Values of P**

Groups Compared	Serum Agglutinins		Fecal Agglutinins	
	Patients with Titers		Patients with Titers	
	$\geq$1:20	>1:80	$\geq$1:15	>1:60
Infants with epidemic diarrhea and controls <1 mo.	>0.050	>0.050	0.004	>0.050
Infants with sporadic diarrhea and controls >1 mo.	>0.050	>0.050	0.037	>0.050

* P values greater than 0.050 are not statistically significant in this instance (Fisher, R. A.: Statistical Methods for Research Workers, ed. 8, New York, G. E. Stechert & Company, 1941, p. 94, paragraphs 21 and 22).

This higher incidence of fecal agglutinins in infants with diarrhea when compared with normal infants is, statistically, of probable significance ($P = 0.037$).[10] Although fecal agglutinin titers greater than 1:60 did occur more frequently in babies with diarrhea than in well babies, this increased incidence was not statistically significant in either age group.

In chart 3 a comparison is made of the maximum fecal agglutination titer of each patient in the two groups of patients studied, well babies and babies with diarrhea. It is apparent from this chart that in babies under 1 month of age fecal agglutinating substances for homologous coliform organisms occurred only in association with diarrhea. On the other hand, in babies over 1 month of age variable titers of fecal agglutinating substances occurred in the absence of diarrhea, as well as in its presence. It is to be noted that in 5 babies with diarrhea fecal agglutinins were absent.

10. The value for P indicates the probability of chance occurrence.

The occurrence and the titer of both serum and fecal agglutinating substances for homologous coliform organisms were compared with the clinical course of diarrhea in each patient. Of the 20 babies with diarrhea only 2 showed a significant rise in the serum agglutinating titer during the course of illness. Both these babies had epidemic diarrhea. The remaining patients showed either no response or serum titers which fluctuated in a manner not clearly correlated with the course

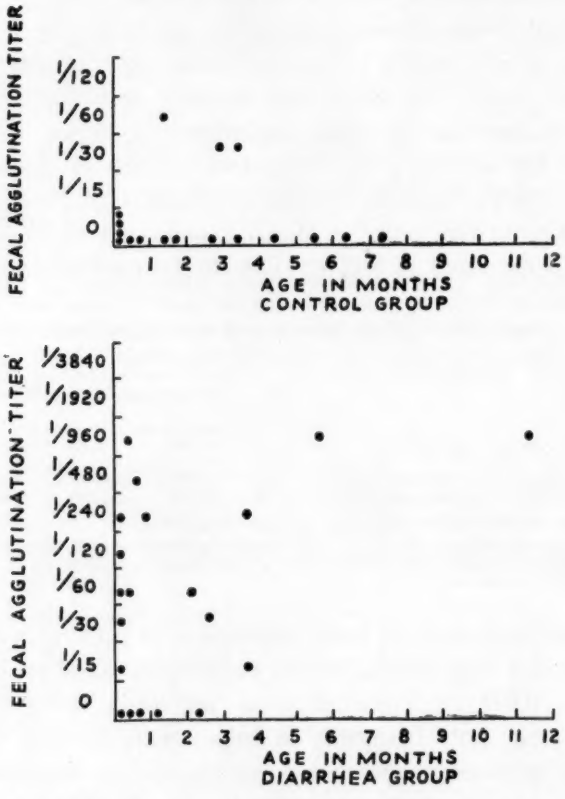

Chart 3.—Comparison of the maximum fecal agglutination titer of each patient in two groups of patients.

of the disease. No fluctuations of serum titers were noted in the control patients from whom multiple samples were obtained.

Fecal agglutinating substances, when detectable, appeared during the acute stage of diarrhea or in the first six days of convalescence. The titers fluctuated in each patient, but no correlation could be demonstrated between these fluctuations and the clinical course of the diarrhea. Fecal agglutinins were not detected in any of the samples from the control patients studied serially.

COMMENT

The finding of serum agglutinins for homologous coliform organisms in similar incidence and range of titer in both normal infants and babies with diarrhea was not anticipated. This observation was particularly striking in the patients over 1 month of age. In babies under 1 month of age the presence of transplacentally received agglutinins would be anticipated. Above the age of 1 month passively transferred agglutinins should be absent. The frequency of elevated serum titers in the older babies, especially those in the control group, suggests that young infants are stimulated to antibody formation by their own enteric organisms more frequently than has been supposed.

The fact that the incidence of serum agglutinins for homologous organisms was not significantly different in the control group and in the babies with diarrhea suggests three possible explanations: (*a*) Coliform organisms are rarely involved in the pathogenesis of the disease, (*b*) the serologic response of infants with infection varies with the individual infant [5b] and (*c*) serum agglutinins are not a good measure of past enteric infection. Information on the latter possibility has been afforded by the work of Watt and DeCapito [11] and Cooper and Kellen [12] in studies on dysentery. The first two authors concluded that the determination of serum agglutinins for dysentery bacilli did not provide a reliable means of diagnosing past enteric infection with the organism, nor did it provide an index of immunity or susceptibility to the disease. The second group of investigators found serum agglutinins for dysentery bacilli in only 25 per cent of 12 children 6 months to 11 years of age convalescent from proved dysentery. All these children had mouse protective antibodies in their serum, but these levels did not correlate either with serum agglutinin titers or with the patient's age. These observations, together with the observations reported in this paper, suggest that the measurement of serum agglutinins for homologous coliform organisms is not a worth while procedure to use in investigating the role played by coliform bacilli in infantile diarrhea of unknown origin.

In our present state of knowledge the presence of agglutinating substances in the feces is difficult to interpret. Their origin is not known with certainty, although two sources are postulated: (*a*) a transudate from extracellular fluid and (*b*) local formation by reticuloendothelial cells in the intestinal wall.

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11. Watt, J., and DeCapito, T. M.: Studies of the Acute Diarrheal Diseases: XV. The Agglutination Test in Shigella Paradysenteriae Infections, Pub. Health Rep. **60**:642, 1945.

12. Cooper, M. L., and Kellen, H. M.: Studies in Dysentery: II. Humoral Antibody Content of Sera from Children Convalescent from Dysentery, J. Immunol. **58**:357, 1948.

Burrows and Havens [4] observed in guinea pigs that passively transferred antibodies, given either by mouth or intravenously, could cross the intestinal wall in either direction. They noted in both human beings and guinea pigs that the titers of fecal and serum agglutinins fluctuated independently of one another. From this independent behavior they inferred that fecal and serum agglutinins were produced at different sites in the body.

In the present study of babies with idiopathic diarrhea it was observed that serum and fecal agglutinin titers fluctuated independently of one another. However, fecal agglutinins appeared either with active diarrhea or within the first six days of convalescence, and they were usually accompanied with a demonstrable titer of serum agglutinins. In only 2 patients were fecal agglutinins observed in the absence of a demonstrable titer of serum agglutinins, but in these infants it is possible that serum agglutinins were present in a lower titer than that measured, i.e., 1:20. Three of the 5 babies with diarrhea and absent fecal agglutinins had measurable serum agglutinin titers (1:20 to 1:80). All 3 babies had mild attacks of epidemic diarrhea of the newborn. Thus, it is probable, until proved otherwise, that fecal agglutinins in idiopathic diarrhea of babies are the result of a transudation of serum across the wall of a hyperemic intestine and that these agglutinating substances are not necessarily locally formed. Methods of investigation other than those already used will be needed to elucidate this problem.

The quantitative significance of the titers of fecal agglutinins has been questioned. In our own experience high or low titers were observed to be excreted in either diarrheal or formed stools. This led us to believe that some factor other than a constant rate of excretion and mere dilution controlled the fluctuations in observed titers. This factor would appear to be a temporary increase in the rate of local excretion or formation of the agglutinating substances.

A well substantiated relation between intestinal coliform organisms and idiopathic diarrhea in babies cannot be described from the results of this investigation.

CONCLUSIONS

1. Substances capable of agglutinating coliform organisms obtained from the baby's intestinal tract occurred in the serum of 76.4 per cent of 17 healthy infants and in 80 per cent of 20 infants with idiopathic diarrhea.

2. Agglutinating substances for homologous coliform organisms occurred in the feces of infants with epidemic diarrhea of the newborn and in infants with sporadic diarrhea in 75 per cent of 20 babies studied. This incidence is significantly greater than the incidence of the same substances in the feces of healthy infants.

3. The occurrence and titer of serum agglutinins for homologous coliform organisms could not be consistently correlated with the clinical course of idiopathic diarrhea in infants.

4. Fecal agglutinins for homologous coliform organisms appeared during the acute stages of diarrhea or in early convalescence. The fluctuations of titer could not be correlated with the clinical course of diarrhea.

5. Observations recorded in this study lend support to the contention that fecal agglutinating substances are the result of a transudation of extracellular fluid across the intestinal wall.

6. This investigation yielded no conclusive evidence of the role played by coliform organisms in infantile diarrhea of unknown origin.

Dr. Edward C. Curnen Jr. advised in the preparation of this report. Dr. Johannes Ipsen, Department of Pharmacology, Yale University School of Medicine, aided in the statistical analysis of the material.

University of Kansas Medical Center, Kansas City (3), Kan. (Dr. Rabe).

MANDIBULAR GROWTH DISTURBANCE IN RHEUMATOID ARTHRITIS OF CHILDHOOD

MILTON B. ENGEL, D.D.S., M.S.
JULIUS RICHMOND, M.D., M.S.
AND
ALLAN G. BRODIE, D.D.S., Ph.D.
CHICAGO

THE RELATIONSHIP of the mandibular condyle to mandibular growth and its significance in certain types of mandibular deformities were discussed in earlier publications.[1] The following study was initiated when it was noted that some of these mandibular disturbances occurred in patients with rheumatoid arthritis. In order to study this relationship further, any cases of rheumatoid arthritis in children admitted to the University of Illinois Hospitals or Clinics during the past year were studied by the orthodontia department concurrent with their pediatric management. As a result, 6 children manifesting mandibular involvement during the course of rhematoid arthritis were available for study.

MATERIAL AND METHOD

All the patients, with one exception, received a thorough physical examination. Lateral and frontal cephalometric roentgenograms were made with the use of the Broadbent-Bolton cephalometer. This technic permits production of relatively undistorted films which can be duplicated, since the relation of head to film to tube is fixed. These roentgenograms were supplemented by laminagrams of the temporomandibular joint. In addition, the extent of the arthritic process was investigated by roentgenograms of other joints.

Tracings of the headplates were made on transparent paper. This permitted analysis of the relationship of the mandibular component to the rest of the face and cranium. The following planes were established (fig. 1): (1) mandibular plane, formed by a line joining gonion and gnathion; (2) sella-nasion (*S-N*) plane, formed by a line joining the center of sella turcica and nasion; (3) nasion-gnathion

From the Departments of Orthodontia and Pediatrics, University of Illinois Colleges of Dentistry and Medicine.

1. Brodie, A. G.: Behavior of Normal and Abnormal Facial Growth Patterns, Am. J. Orthodontics **27**:633-647 (Nov.) 1941. Engel, M. B., and Brodie, A. G.: Condylar Growth and Mandibular Deformities, Surgery **22**:976-992 (Dec.) 1947.

(*N-Gn*) plane formed by a line joining nasion and gnathion, and (4) sella-gnathion (*S-Gn*) plane formed by a line joining the center of sella turcica and gnathion.

The angles formed between these planes were then measured and compared with the range existing in normal, growing children. It was possible to take additional roentgenograms subsequently in 2 cases, thus permitting a study of growth in the areas involved.

REPORT OF CASES

CASE 1.—A 4 year old white girl, P. S., was admitted to our pediatric service because of swelling of her fingers, toes and knees for the previous one and a half year. The mother stated that the child had a poor appetite until 2 years of age, when a tonsillectomy had been performed because of recurring tonsillitis. Shortly after this, a gradual swelling of the fingers developed, and the toes and knees were similarly involved in the ensuing two months. She had pain on motion of the

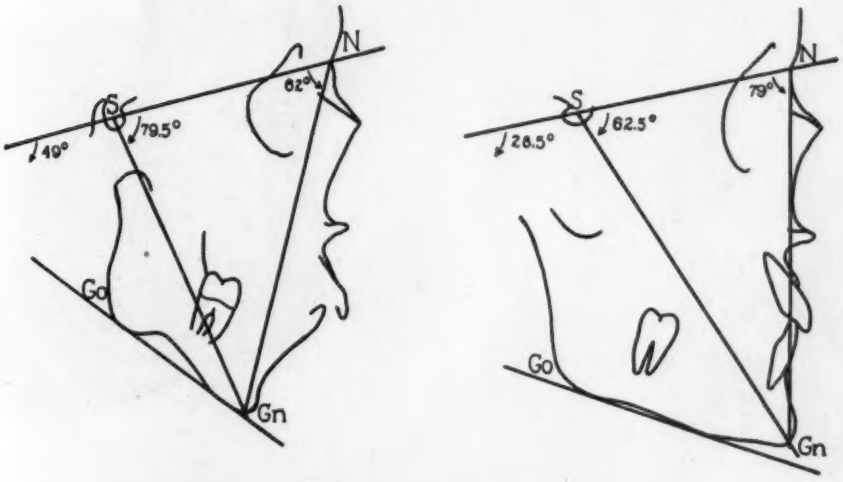

Fig. 1.—Tracings of the lateral roentgenograms of a normal child (right) and of a child with rheumatoid arthritis (left) demonstrating the difference in the skeletal pattern of the face. *Gn* signifies gnathion, *Go*, gonion, *N*, nasion and *S*, sella turcica.

involved joints, but no redness was noted. No temperature readings had been taken by the mother. When the girl was 3 years of age, the mother observed that the child had difficulty in walking on arising in the morning, but the difficulty disappeared after she had been up for a short time. There was no family history of articular disease.

Physical examination revealed a thin, pale white girl of 4 years, who walked with a shuffling gait. Her weight was 35 pounds (15.9 Kg.). There was slight injection of the pharynx, and a moderate amount of lymphoid tissue was observed in the tonsillar fossae. Moderate, generalized enlargement of the lymph nodes was noted. The abdomen was soft; the liver and spleen were not palpable. Moderate fusiform swelling of all proximal interphalangeal joints was present; limitation of motion was slight.

The urinalysis gave normal results. The red blood cell count was 3,600,000 per cubic millimeter, the hemoglobin concentration, 14 Gm. per hundred cubic centimeters and the white blood cell count, 8,400 per cubic millimeter, with 45 per cent polymorphonuclear cells, 47 per cent lymphocytes, 5 per cent monocytes and 1 per cent eosinophils. The sedimentation rate was 11 mm. per hour (Wintrobe). The Mantoux test (1 : 500) gave a negative reaction.

Roentgenograms showed periarticular swelling about the involved joints, but no skeletal pathologic changes. Subsequent roentgenograms have shown, in addition, generalized decreased density of bone without distortion of bony cortical structure, a sign which the roentgenologist stated to be indicative of rheumatoid arthritis. Because of the articular involvement with periarticular swelling, pain and early limitation of motion, a diagnosis of rheumatoid arthritis was made.

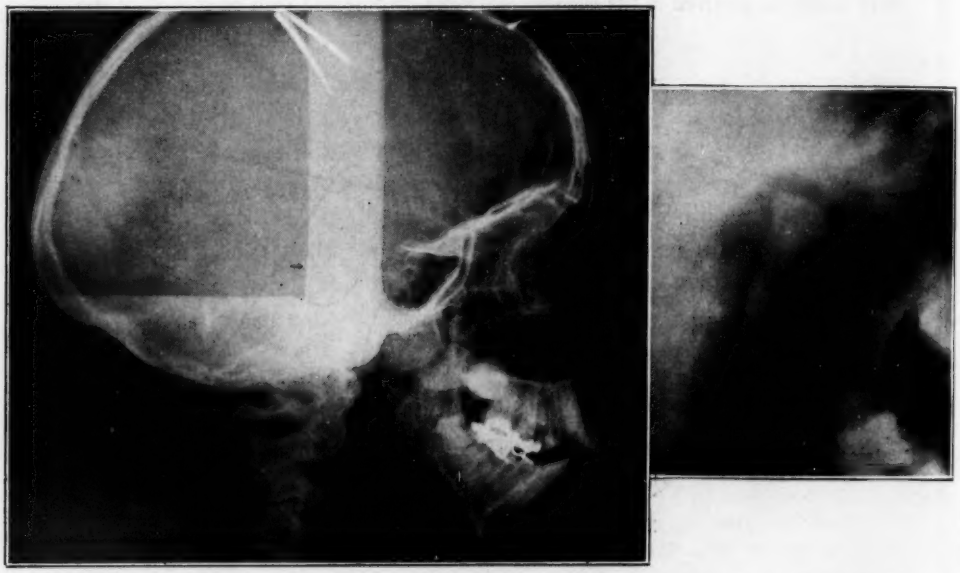

Fig. 2 (case 1).—Left, lateral cephalometric roentgenogram of P. S. at 8 years 1 month of age. Right, laminagram of the temporomandibular joint. The blunting of the condylar surface is characteristic of an advanced arthritic process.

Detailed orthodontic examination of this patient revealed the typical *Vogelgesicht* noted in cases of arrest of growth of the mandibular condyles. All movements of the jaw were possible, but the range was slightly limited. The child had a class II division (Angle's classification) [2] malocclusion with an open bite in the anterior region. The mandibular teeth were somewhat crowded because of inadequate development of the jaw.

The cephalometric roentgenogram (fig. 2, left) revealed a deformed, underdeveloped mandible with typical antegonial notching. Because of the failure in downward and forward growth, the relation between the mandible and the rest

2. This refers to that malrelation of the jaws and teeth in which the upper anterior teeth appear protrusive and the lower jaw appears retruded.

of the craniofacial complex was disturbed. The pharyngeal space was considerably narrowed.

Laminagraphic examination of the temporomandibular joint (fig. 2, right) indicated extensive modification of the condyles. The articular surfaces were sharply flattened. The changes of the temporal surface of the joint were not so clearly visualized. About the area of the joint there was a haziness which is generally associated with fibrotic changes.

Case 2.—I. G., a 5 year old white girl, was admitted to our pediatric service because of pain and stiffness of the knees, fingers and wrists. These symptoms started when the child was 9 months of age, at which time the knees became quite swollen. A physician applied casts to immobilize the knees for three months.

Fig. 3 (case 2).—Lateral cephalometric roentgenogram of I. G. at 12 years 8 months of age.

After the casts were removed, the child learned to walk, although the knees were stiff. At 4 years of age, the patient had measles which was complicated by bilateral purulent otitis media. Following this, her right wrist became swollen, tender and stiff. Four months prior to her admission to the hospital she acquired scarlet fever which was complicated by bilateral purulent otitis media following which pain, tenderness and increased local heat developed in the hands, wrists and knee joints. The mother and father were living and well. Several maternal uncles were said to have had "arthritis."

On physical examination the patient was observed to be thin and somewhat pale. She weighed 36 pounds (16.3 Kg.). The tonsils were moderately large; the pharynx was moderately reddened. The heart and lungs seemed normal. The

liver and spleen were not palpable. The knees, wrists and hands demonstrated fusiform swelling with only mild limitation of motion. The reflexes were normal.

Results of urinalysis were normal except for a trace of albumin; the red blood cell count was 3,920,000 per cubic millimeter; the hemoglobin concentration was 12.2 Gm. per hundred cubic centimeters. The white blood cell count was 12,000 per cubic millimeter, with a differential count of 40 per cent lymphocytes, 6 per cent monocytes, 53 per cent neutrophils and 1 per cent eosinophils. The Wassermann and Kahn reactions were negative. The sedimentation rate (Wintrobe) was 8 mm. in an hour. The Mantoux reaction (1:1,000) was negative. Roentgenograms of the hands and wrists demonstrated periarticular swellings about the involved joints, but the surfaces of the joints seemed normal. The history of chronic articular pain and swelling, along with the physical findings and roentgenologic evidence of periarticular swelling, led to a diagnosis of rheumatoid arthritis.

This patient had the characteristic facial appearance of a bilateral condylar arrest, i. e., the decidedly receded chin and convex facial profile. She was capable of performing all the normal movements of the jaw, although there was some restriction in their range. The occlusion was characteristic of a class II division 1 malocclusion. Because of the failure in growth of the jaw, there was inadequate development of the alveolar arch to accommodate a regular arrangement of teeth.

The mandible was retarded in its development (fig. 3) and serial records indicated that it had not changed in size in the period of a year. This was observed by superposing the tracings. The contour of the bone was modified, and the typical bowing and antegonial notching were noted. As a result, the relation of the mandible to the rest of the craniofacial complex was abnormal. The growing tongue was encroachng on the pharyngeal airway.

Laminagraphs of the joint revealed a shortened condylar process. The articular surface was flattened and appeared somewhat eroded. The temporal surface of the articulation was also flat. No articular eminence was demonstrable. It would be impossible to eliminate completely the otitis media as a possible contributing factor to the condylar arrest, although it is our opinion that this injury was part of the generalized articular disease.

CASE 3.—A 4 year old white girl, C. L., was first seen in our outpatient clinic because of pain, swelling and tenderness of various joints. The parents stated that the child had been perfectly well until 9 months of age when it was first observed that her neck was somewhat stiff and painful on motion. This persisted, and at 18 months all joints of the extremities became swollen and painful, but no redness was noted. At this time, the patient perspired profusely during sleep but no temperature readings were taken. The joints of the extremities and back continued to be involved intermittently as described, resulting in a forward flexion of the trunk, stiffness of the neck and moderate flexion deformities of the wrists. There had been no gain in weight since 2 years of age. There was no family history of articular disease.

On physical examination the patient was observed to be somewhat thin and pale. She weighed 25½ pounds (11.5 Kg.). The chest was slightly funnel shaped, with more bulging on the left. Slight dorsal scoliosis in the lower left region and generalized fusiform enlargement of joints with limitation of motion and deformity were noted; there was flattening of the lumbar curve. The liver and spleen were not palpable.

Urinalysis showed normal results. The red blood cell count was 3,800,000, and the white blood cell count, 6,200 per cubic millimeter, with a differential count of 51 per cent polymorphonuclear cells, 2 per cent monocytes, 46 per cent lymphocytes and 1 per cent eosinophils. The sedimentation rate was 30 mm. in one hour (Wintrobe). Wassermann and Kahn reactions were negative. The Mantoux test (1:1,000) gave a negative reaction. The roentgenograms demonstrated a moderate list of the thoracolumbar part of the spine to the left. Roentgenographically, the density of all bones was moderately decreased. Valgus deformity of both knees was present, with bowing of both tibial shafts. Generalized muscular atrophy and periarticular swelling about both knees were observed. There was moderate irregularity of contour, suggesting beginning loss of substance of the head of the first metatarsal bilaterally, which semed characteristic of

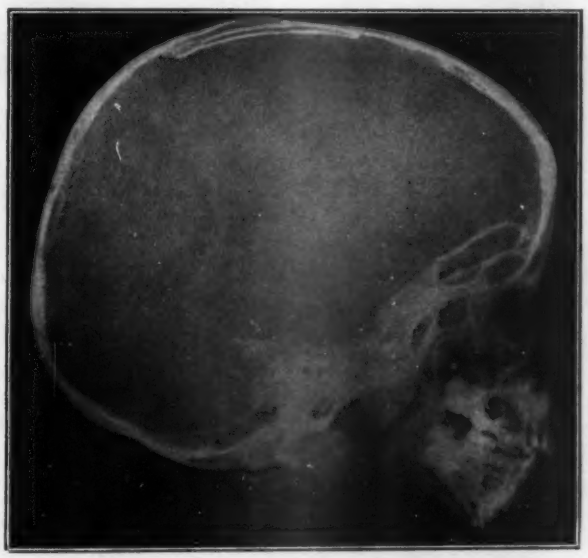

Fig. 4 (case 3).—Lateral cephalometric roentgenogram of C. L. at 4 years 2 months of age.

rheumatoid arthritis. The articular surfaces of the elbows and the joints of the hands were irregular, demonstrating numerous areas of erosion. Because of the history, physical findings and characteristic roentgenologic signs, a diagnosis of rheumatoid arthritis was made.

Since this patient is the youngest of the series, the deformity was not as prominent as that of the others. The child had a class II division 1 malocclusion. All movements of the mandible could be executed, but the range was slightly restricted. The cephalometric roentgenogram (fig. 4) revealed the typical pattern seen in condylar arrests with an increased angle between the mandibular plane and the cranial base and an acute angle between the nasion-gnathion plane and the cranial base. The mandible was smaller than that usually seen at this age. Laminagraphs of the temporomandibular joints showed flattening of the temporal surface of the fossa and of the head of the condylar process. There was some

haziness about the right joint characteristic of the periarticular fibrosis. No translatory movement of the condyle was demonstrated on opening.

CASE 4.—G. G., a 9 year old white girl, was referred to us because of pain, swelling and deformity of numerous joints. The history revealed that the patient had scarlet fever at 6 months of age; recovery had been uneventful. At 17 months of age the mother noted that the child began to limp and was unable to move the right knee through a full range of motion. At 18 months she had a rash which was again considered to be scarlet fever. The right knee continued to be the only joint manifesting symptoms until the patient was 4 years of age, when, within several weeks, she showed pain, swelling and limitation of motion of the joints of the hands and feet. Pain and limitation of motion of the spine, particularly in the cervical region, developed. The appetite became poor and gain in weight was extremely slow. The deformities of the joints gradually became more pronounced, and the patient displayed weakness and easy fatigability. Vitamin D in doses of 100,000 units orally was administered daily from the development of symptoms at 4 years of age to the time of her admission to the hospital (a total of five and one half years) with no beneficial results.

On physical examination the child was observed to be rather thin and undersized with multiple deformities of the joints. The weight was 33 pounds (15 Kg.) and the height 45 inches (114 cm.). The head was tilted to the right but could be moved to the left. The cardiac findings were normal. The spleen was palpable 3 cm. inferior to the left costal margin and was firm. The liver was not palpable. The extremities were very thin; severe muscular atrophy was observed. There was fusiform swelling of all joints of the fingers; moderate swelling about the ankles, knees and wrists was observed with considerable limitation of these joints. The patient walked with a shuffling gait.

The urinalysis revealed a specific gravity of 1.012; there was a trace of albumin. The nonprotein nitrogen varied between 41 and 63 mg. per hundred cubic centimeters of blood and the urea nitrogen was 15 mg. per hundred cubic centimeters of blood on several occasions. The total serum proteins were 8 per cent, with 4.9 per cent albumin and 3.1 per cent globulin. The cephalin flocculation was 1 plus in forty-eight hours. The red blood cell count was 4,350,000 and the white blood cell count, 7,000 per cubic millimeter, with a differential count of 85 per cent polymorphonuclear cells, 2 per cent monocytes and 13 per cent lymphocytes. The hemoglobin concentration was 12.5 Gm. per hundred cubic centimeters; the sedimentation rate was 20 mm. in an hour (Wintrobe). The Wassermann and Kahn tests gave negative reactions. The electrocardiogram was within normal limits. The Mantoux reaction (1:1,000) was negative.

Roentgenograms indicated narrowing of the joint spaces of the knees with noticeable calcifications of the popliteal arteries. The lateral aspects of the femoral and tibial epiphyses were irregular in contour. The cervical portion of the spine demonstrated irregular ossification and contour. Roentgenograms of the hands and wrists revealed distortion of the angle of the distal part of the ulna and radius, moderate destruction and deformity of the carpal bones, thinning and irregularity of the epiphyses of the proximal phalanges and decided loss of density through all the bones of the hands and forearms. The clinical course of the patient's illness, the physical and roentgenographic findings of abnormal renal

function and the prominent arteriosclerotic changes observed in the roentgenograms will be discussed in a separate publication.

The facial deformity was mild; the child had a malocclusion characterized by an open bite. All mandibular movements were possible with only slight restriction of range. The mandibular changes were least pronounced in this patient (fig. 5, upper part). However, the pattern was a dysplastic one, as indicated by visual examination as well as by comparison of the critical angular measurements with those of normal range. There was only slight antegonial notching. It is probable that the temporomandibular joints had only recently been involved; thus, there had been but moderate retardation of mandibular growth at this time. Roent-

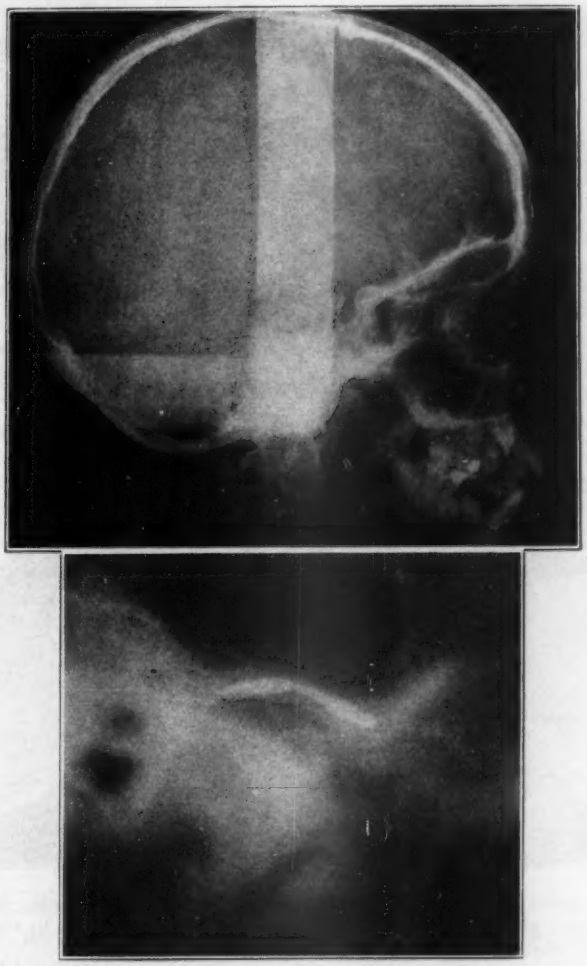

Fig. 5 (case 4).—Upper, lateral cephalometric roentgenogram of G. G. at 9 years 9 months of age. Lower, laminagram of the temporomandibular joint. Note the erosion of the condylar head and the haziness about the joint characteristic of periarticular fibrosis.

genograms of the temporomandibular joints showed some flattening and erosion of the head of the condyle (fig. 5, lower part), indicative of recent involvement. The changes were not as extensive as those observed and illustrated in case 1. Periarticular changes were suggested by haziness about the area of the joint.

CASE 5.—A 16 year old white girl, B. S., was observed by us because of an increasingly apparent deformity of the mandible, limitation of motion of the neck and listlessness. Chickenpox and measles had occurred in early childhood. There had been no history of disturbances of the joints; no obscure febrile illness

Fig. 6 (case 5).—Lateral profile photographs of B. S. These illustrate the progressive deformity which occurred over a period of eleven years due to the involvement of the condylar growth centers. The photographs correspond to the roentgenograms of figure 7.

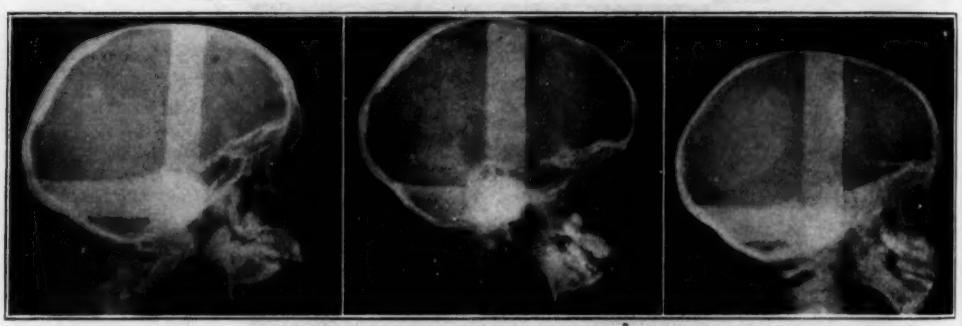

Fig. 7 (case 5).—Lateral cephalometric roentgenograms of B. S., demonstrating the progressive alteration of the skeletal pattern (ages from left to right, 15 years 9 months, 12 years 6 months and 4 years 6 months).

had been experienced. This child had lived in an orphanage from the age of 3 years, and, since this group of children was being screened for orthodontic problems regularly, it was our good fortune to have photographs of the child at intervals which indicated that the mandibular deformity was not congenital and that it had developed gradually.

On physical examinatoin the patient appeared thin and somewhat apathetic. Her height was 60 inches (152 cm.) and her weight 74 pounds (33.6 Kg.). An obvious recession of the mandible was observed. Rotation of the child's neck was

limited to a range of approximately 10 degrees on the right and 45 degrees on the left. The breasts were normally developed. The cardiac findings were entirely normal. The liver and spleen were not palpable. No deformities of the joints of the extremities were observed.

Laboratory findings were as follows: The red blood cell count was 4,980,000 per cubic millimeter, the hemoglobin concentration, 13.8 Gm. per hundred cubic centimeters and the white blood cell count, 11,300 per cubic millimeter, with the differential count consisting of 62 per cent polymorphonuclear cells, 5 per cent eosinophils, 1 per cent basophils and 32 per cent lymphocytes. The serologic reactions were negative and urinalysis gave normal results.

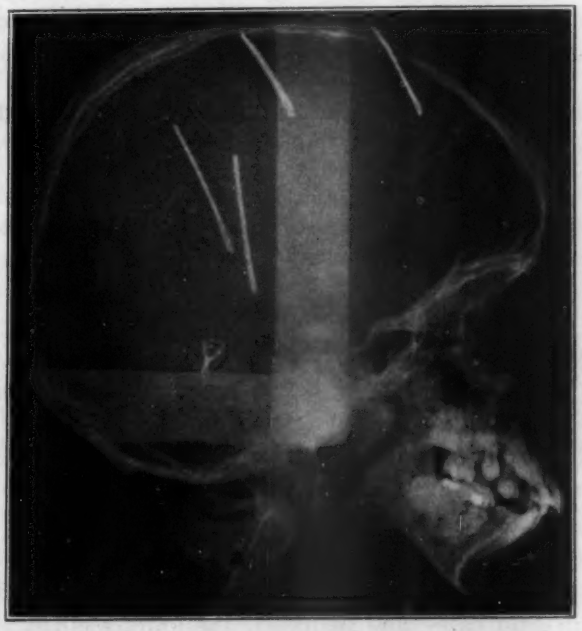

Fig. 8 (case 6).—Lateral cephalometric roentgenogram of J. F. at 10 years 11 months of age.

On roentgenographic examination the cervical portion of the spine was irregularly calcified; the intervertebral spaces were irregular and narrowed, bony margins were irregular, and generalized decreased density was noted. The bone age was normal.

The history, physical, roentgenologic and laboratory findings led us to diagnose the condition as rheumatoid arthritis involving the cervical part of the spine and the temporomandibular joints. The first dental examination of this child was made at the age of 4½ years. Cephalometric roentgenograms were taken and, though these were suggestive of abnormality, the discrepancy was not noted at the time. Eight years later further records were made. At that time the characteristic changes associated with arrested mandibular development were prominent.

The occlusion was definitely affected; the roentgenographic changes were serious and typical, i. e., with antegonial notching, mandibular underdevelopment and dysplastic relation between the cranium and the lower portion of the face. Further study and records followed in three more years. The change in relations between the mandible and the upper part of the face and cranium had become more accentuated. The deformity was a progressive one, and the malocclusion had become even more pronounced. Since the soft structures of the floor of the month had continued growing while osseous development had been retarded, there was evidence of some narrowing of the pharyngeal space. The progressive nature of the dysplasia is strikingly presented in the accompanying figures (figs. 6 and 7).

Later laminagraphs of the temporomandibular joint showed considerable periarticular involvement which obscured the contours of the condyle. Associated with this was some limitation in the range of the mandibular movements.

CASE 6.—An 11 year old girl, J. F., was seen by members of the orthodontic department. A diagnosis of rheumatoid arthritis had been made in this case in infancy. There was clinical evidence of multiple joint involvement. Enlargement of the interphalangeal joints was particularly evident. Unfortunately, the patient was not available for further pediatric examination. The clinical examination revealed bilateral notching, prominent malocclusion and the *Vogelgesicht*. Cephalometric roentgenograms over a two year period (fig. 8) showed typical findings analogous to those which have been described in the preceding cases.

SUMMARY OF OBSERVATIONS

When temporomandibular involvement occurs in rheumatoid arthritis of childhood, the pattern of the jaw disturbance appears characteristic. All patients in our group demonstrated the typical *Vogelgesicht*. Palpation of the inferior mandibular border revealed the presence bilaterally of notching at the junction of the body and ramus. These patients were able to execute all movements of the jaw; however, the range of movement was somewhat restricted. All had a class II division 1 malocclusion. The upper incisors appear protrusive; the bite opened anteriorly in most cases, and frequently the lower teeth were crowded.

Roentgenographic analysis was more revealing. The mandible was deformed and failed to attain its full growth potential. The height of the ramus was reduced and the body was shortened. Measurement of the angular relation between the mandible and the rest of the craniofacial complex emphasized this (fig. 1). Thus, in all cases the nasion-sella-gnathion angle was larger than the normal range; the sella-nasion-gnathion angle was more acute and the angle formed between the lower border of the mandible and the cranial base was greater than that formed in the normal jaw. These changes merely reflected failure of downward and forward mandibular growth. Frequently, the pharyngeal space was narrowed because of encroachment of the growing tongue.

Laminagrams of the temporomandibular joint (figs. 2, right, and 5, lower) showed more clearly the localized changes. The condyles were flattened and stunted, and occasionally in early stages one could see evidence of erosion. The temporal surface of the joint suffered loss of contour and was flattened. Frequently, there was a haziness about the area of the joint which was associated with periarticular fibrosis.

In patients for whom serial records were available it was noted that the incremental growth of the mandible was decidedly retarded, whereas the other structures of the face continued their growth. Records collected for long periods indicate that the deformity can be progressive.

COMMENT

Although chronic arthritis in children was first described by Cornil [3] in 1864, it was not until the description by Still [4] in 1897 that this condition was recognized as a disease entity in children. It is obvious now, however, that the syndrome of chronic arthritis and generalized lymphadenopathy, accompanied with signs of systemic reaction and visceral changes (especially splenomegaly), which has generally come to be regarded as Still's disease, included only the severer forms of what is now regarded as the childhood counterpart of rheumatoid or atrophic arthritis of the adult.

Our attention was directed to this disease when we observed mandibular deformities for which therapy was desired in children manifesting the typical findings of rheumatoid arthritis. Although the exact incidence of rheumatoid arthritis in children is difficult to determine (Coss and Boots [5] reported that 4.9 per cent of all patients with rheumatoid arthritis seen in their clinic were children), our experience and that of Pickard [6] indicate that it is somewhat commoner than heretofore recognized. We are now more cognizant of the fact that this form of arthritis may be monoarticular, especially at the onset. Lack of recognition of this has undoubtedly been responsible for failure

3. Cornil, V.: Mémoire sur les coïncidences pathologiques du rhumatisme articulaire chronique, Compt. rend. Soc. de Biol. **1** (pt. 2): 3-25, 1864.

4. Still, G. F.: On a Form of Chronic Joint Disease in Children, Med.-Chir. Tr. **80**:47-59, 1896-1897.

5. Coss, J. A., and Boots, R. H.: Juvenile Rheumatoid Arthritis, J. Pediat. **29**:143-156 (Aug.) 1946.

6. Pickard, N. S.: Rheumatoid Arthritis in Children, Arch. Int. Med. **80**:771-790 (Dec.) 1947.

to diagnose cases early in the past, when they were usually attributed to tuberculosis or other specific etiologic factors.

The incidence of involvement of the temporomandibular joint in the cases described by Still [4] was 14 per cent. In a more recent study of a larger series,[6] 17 per cent showed temporomandibular involvement. This is generally determined by study of mandibular movement rather than by consideration of growth dysplasia. In our series it was noted that the latter was a much more prominent feature than the functional impairment; hence we believe that the previously recorded incidence of temporomandibular involvement does not necessarily reflect the true incidence of such involvement in rheumatoid arthritis of childhood.

The temporomandibular joint may be the first to be affected. One of our recent patients, not reported on with this group, gave a clinical impression of rheumatoid arthritis, but the laboratory findings were inconclusive. There were mandibular changes characteristic of arthritic involvement of the temporomandibular joint, and only recently the patient has begun to complain of some pain and swelling in the wrists, ankles and knees, which we believe corroborates our impression of rheumatoid arthritis. These observations indicate that the temporomandibular joint may be involved early in the course of the disease.

To the orthodontist this has special significance, since he may on occasion examine a child with rheumatoid arthritis in whom the only joint involved is the temporomandibular. When confronted with mandibular deformities in childhood, one should, therefore, be cognizant of this etiologic possibility and not designate all these deformities as congenital in origin, in spite of the fact that the patient may be observed at an early age.

The residual involvement of the joints from a functional point of view is related to the joints involved. Thus, while the function of the knees is recovered to a considerable extent in many cases, the elbows and wrists usually show more residual deformity and functional loss. In one series of 6 patients [6] with temporomandibular involvement, 5 showed residual defects of joints, although none demonstrated ankylosis.

The pathogenesis of the mandibular deformity may be understood if one considers the role of the condyle in normal mandibular development. This site is probably the most active center in the growing jaw. The histologic aspects of the area were described by Toldt [7]

7. Toldt, C.: Ueber das Wachsthum des Unterkiefers, Ztschr. f. Heilk. **5**:1-14. 1884.

and Charles [8] and more recently again by Sicher and Weinmann [9] and others. This center appears in the 50 mm. stage of the embryo and its activity attains a maximum during the prenatal period.

Microscopic examination of this area (fig. 9) reveals the presence of three zones: (1) chondrogenic, (2) cartilaginous and (3) osseous. The condyle is capped by a narrow layer of fibrous tissue which contains connective tissue cells and a few cartilage cells. The inner layer of this covering is chondrogenic, giving rise to hyaline cartilage cells which constitute the second zone. There is interstitial proliferation of

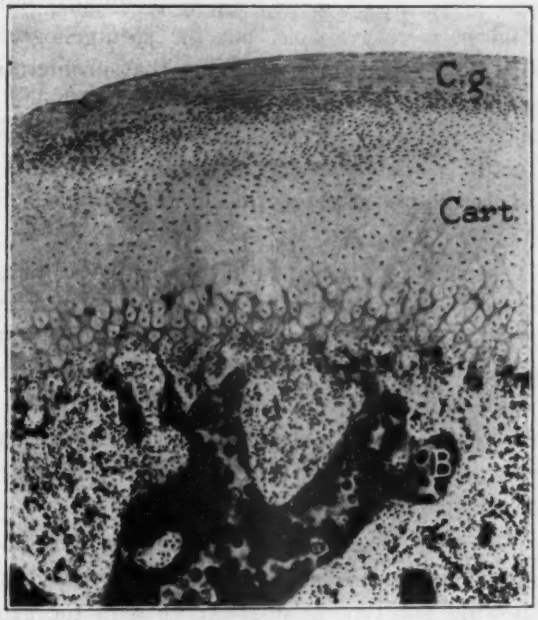

Fig. 9.—Section through the condyle of a newborn child. The three zones described in the text are shown. *C.g.* signifies chondrogenic zone, *Cart.*, cartilage and *B*, bone (Sicher and Weinmann [9]).

the cartilage, and in the third zone one observes ossification occurring around the cartilaginous scaffolding. The picture is analogous to that observed in the endochondral epiphysial ossification of a long bone.

The condylar growth center maintains its activity longer than most other centers in the head, persisting until at least the twentieth year.

8. Charles, W.: The Temporo-Mandibular Joint and Its Influence on the Growth of the Mandible, Brit. Dent. J. **46**:845-854 (July 15) 1925.

9. Sicher and Weinmann, in Orban, B.: Oral Histology and Embryology, St. Louis, C. V. Mosby Company, 1944.

This provides the forward and downward vector for mandibular growth and contributes as well to increased width of the jaw.

The pathologic changes of chronic arthritis of children have been reviewed by Portis.[10] In his series he showed that erosion of the cartilaginous articular surface may occur. Such a change and the concurrent disturbance in vascularity exert a depressing effect on proliferation of cartilage in adjacent epiphyses. Kuhns and Swaim [11] pointed out that frequently premature ossification occurred in such epiphyses, resulting in definite retardation of growth in the affected limbs.

No histologic preparations of the temporomandibular joint in chronic arthritis in children were available, but the roentgenograms provided us with findings which sustained the belief that proliferation of cartilage in the condylar head was disturbed. This probably occurred in much the same manner as the other involvements of joints. Since this joint structure is so critically important in normal mandibular development, a resultant strikingly localized craniofacial dysplasia is to be expected.

Analysis of serial records of some of our patients indicated that the adjacent structures, such as those of the upper part of the face, may continue to grow while the mandible remains relatively static. Since the tongue and structures in the floor of the mouth continue to develop while the mandible fails to move forward, encroachment on the pharyngeal space may result. The disease serves then to demonstrate selectively the importance of the growth center in the condyle for normal mandibular and facial development.

Although the facial deformity is characteristic, it is not to be considered pathognomonic, since such a change of mandibular contour may occur following any type of interference with the growth activity of both condyles. However, our experience leads us to believe that rheumatoid arthritis should be suspected whenever this type of facial deformity is seen.

CONCLUSIONS

1. Rheumatoid arthritis of childhood may involve the temporomandibular joint. This may be the first joint to manifest clinical symptoms.

2. The condylar area, an important growth site, may be injured by the inflammatory reaction. The changes in the joint can be visualized with the laminagram.

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10. Portis, R. B.: Pathology of Chronic Arthritis of Children (Still's Disease), Am. J. Dis. Child. **55**:1000-1017 (May) 1938.

11. Kuhns, J. G., and Swaim, L. T.: Disturbances of Growth in Chronic Arthritis in Children, Am. J. Dis. Child. **43**:1118-1133 (May, pt. 1) 1932.

3. Growth of the mandible may become definitely decelerated because of the inhibitory effect of the arthritic process on proliferation of cartilage and ossification.

4. Continued growth of the soft structures of the floor of the mouth, particularly the tongue, associated with the retarded forward and downward movement of the mandible, frequently results in encroachment on the pharyngeal space.

5. The pathogenesis of the facial deformity and disturbed relationship of the jaws and dental arches is discussed.

808 South Wood Street (12).

Case Reports

TYPHOID MASKED BY MEASLES

Perforation of Intestine with Recovery

ROBERT ORR WARTHEN, M.D.
WASHINGTON, D. C.

PERFORATIONS of typhoid ulcers are probably the most dreaded of all complications of typhoid and have been estimated to occur in 2 to 3 per cent of all cases.[1] The points of perforation (usually multiple, but occasionally single) are generally in the ileum; however, they also occur in the cecum, colon, gallbladder and appendix. Of those extremely rare cases of typhoid cholecystitis, the incidence of perforations of gallbladder ulcers has been reported as high as 46 per cent.[2] Perforations of typhoid ulcers in infants and children account for approximately 30 per cent of the total mortality from typhoid.[1b] The mortality rate for perforated typhoid ulcers is estimated at 33.4 to 50 per cent when surgical treatment is given; however, without surgical intervention this rate approaches 100 per cent.[3]

The case herein reported represents one of intestinal perforation with recovery. It is unique in that the symptoms of typhoid were masked by an attack of measles and the perforation occurred while the patient was under observation for measles and before typhoid was diagnosed or suspected.

REPORT OF A CASE

R. K., a 7½ year old white girl, was admitted to the Children's Hospital on Feb. 4, 1948 because of dyspnea, vomiting, abdominal pain and diarrhea. She had apparently been well until five days prior to her admission, when measles developed. Measles also developed in 2 of her siblings on the following day.

Three days before her admission, the patient experienced a mild, persistent periumbilical pain accompanied with a profuse yellow to brown watery diarrhea, with stools occurring every half hour to two hours. A mixture of kaolin and pectate kaopectate® (an absorbent preparation for intestinal dysfunction) was given and other symptomatic measures were employed; in spite of this therapy the diarrhea and abdominal pain persisted with equal severity until her admission. The measles rash had subsided by the day prior to her admission.

During the early morning hours of the day of her admission, the child experienced a sudden, sharp, generalized abdominal pain and shortly thereafter vomited "bile." The pain and vomiting continued throughout the day and were prominent at the time of her admission.

From the Children's Hospital.

1. (*a*) Hutcheson, A. C.: Typhoid Perforations: Report of Five Cases, China M. J. **41**:559 (June) 1927. (*b*) Muir, J. B. G., and Chia, S. C.: Perforated Typhoid Ulcer: Note on Three Successful Cases, Brit. M. J. **1**:976 (June 6) 1931.

2. Liège, R., and Folliasson, A.: Medical and Surgical Study of Perforations of the Gall Bladder During the Course of Typhoid Fever in Children, Arch. de méd. d. enf. **34**:581 (Oct.) 1931.

3. Footnote 1. Liège and Folliasson.[2]

There had been no known contact with contagious or infectious diseases. Neither the patient nor any member of her family had been out of the city during the previous year, and they had never consumed unpasteurized dairy products. The family history was irrelevant.

Her past history revealed that she had had chickenpox and whooping cough during her infancy and had been subject to frequent "colds" and coughing spells. Three previous hospitalizations at Children's Hospital had been recorded, the first being at 7 weeks of age for a period of eight days with a diagnosis of pneumonia of the lower lobe of the left lung, the second being at 5 months of age for a period of six days with a diagnosis of acute nasopharyngitis and the third at 18 months of age for a period of eleven days because of ingestion of an unknown "poison"; all illnesses were without complications. No immunizations had been performed other than those for diphtheria and smallpox at the age of 5 years.

Physical examination on her admission to the hospital revealed a poorly developed and nourished white girl in moderately severe respiratory distress who appeared pale, toxic and dehydrated. Her pulse rate was 160 per minute, respirations were 56 per minute; blood pressure was 110 systolic and 70 diastolic; temperature was 104 F. (rectum), and her weight was 42 pounds (19.1 Kg.). The oropharynx was mildly inflamed, the remainder of the head and neck being essentially normal. Auscultation of the heart disclosed a sinus tachycardia (160 per minute) and a soft grade 1 systolic murmer heard best at the apex. Examination of the lungs revealed dulness to percussion over the entire lower field on the left, with diminished breath sounds and an occasional crepitant rale in that area. The abdomen was distended, splinted, silent and diffusely rigid with generalized exquisite tenderness, including rebound. Her extremities appeared emaciated and a generalized fine desquamation of the arms was noted (which was attributed to dehydration and possibly to measles). Rectal examination revealed poor sphincter tone and pronounced tenderness in the cul-de-sac, more prominent on the right than on the left. The results of the remainder of the physical examination were essentially normal.

A roentgenogram of the chest taken shortly after her admission disclosed an area of thickened pleura in the peripheral part of the base of the left lung, associated with an early infiltrative process overlying the left side of the diaphragm. A film made with the child in an upright position showed the abdomen to be moderately opaque, with the exception of a distended loop of bowel accompanied with several fluid levels. This appearance was interpreted as being indicative of functional or organic obstruction. The presence of an air bubble under the dome of the right side of the diaphragm was questionable.

She was immediately placed in an oxygen tent and measures were employed to combat the dehydration and acidosis, as well as the apparent peritonitis and pneumonia. The diagnoses of primary peritonitis, peritonitis due to a ruptured appendix and typhoid peritonitis were entertained at that time; however, surgical treatment was delayed because of the extremely critical condition of the patient. Shortly after her admission, her serum agglutinated antigens H and O of Eberthella typhosa in dilutions of 1:20 through 1:80. This titer reached its peak of 1:1,280 on the eighth day in the hospital.

On the following morning, sixteen hours after her admission, the patient appeared well hydrated; however, she remained lethargic, pale and toxic, and the chest and abdominal changes previously noted were more pronounced in degree. Occasional attacks of vomiting occurred until the third day, when a Levin tube was placed in her stomach and Wangensteen suction instituted.

The observations on the chest remained essentially unchanged until the tenth day, when crepitant rales were also detected over the right lower pulmonary field. The abdominal findings were similar to those on admission; however, rectal examination disclosed a soft, rounded, tender mass in the cul-de-sac, with tenderness greater on the right than on the left (interpreted as a pelvic abscess).

On the eleventh day, the entire abdomen suddenly became more rigid and a fluid wave was elicited. This was interpreted as representing an exacerbation of the peritonitis, perhaps due to perforation of additional intestinal ulcers, to extension of the peritonitis or to the breaking through of a walled-off pocket of pus.

Because a progressively enlarging mass in the cul-de-sac was interpreted as a localized pelvic abscess, a laparotomy was performed on the fourteenth day with the patient under anesthesia induced with cyclopropane, oxygen and an anesthetic agent injected into the low spinal region. A McBurney incision was made, and when the peritoneum was opened a thick, creamy, purulent exudate

TABLE 1.—*Results of Cultures Made Throughout Stay in the Hospital*

Day or Days in the Hospital	1	2	3	5	6	8	14	22	34	40	44 & 47	51	53	6
Agglutination of O and H E. typhosa antigens	1:20 through 1:80	..	1:20 through 1:640	..	..	1:20 through 1:1,280	..	..	..	..	..	..	..	
Stool culture for E. typhosa	....	—	....	+	+	..	..	..	..	—	—	—	..	
Blood culture.....	....	—	—	..	—	..	..	..	..	..	..	..	..	
Culture of abdominal exudate	....	..	....	..	..	..	E. typhosa; E. coli	Hemolytic E. coli; pneumococci	Nonhemolytic Staph. aureus; nonhemolytic E. coli	..	..	..	Hemolytic E. coli	
Urine culture for E. typhosa	....	—	....	—	..	..	..	..	..	Nonhemolytic E. coli	..	—	..	

oozed forth. About 800 cc. of this purulent exudate was withdrawn, and because of the presence of a diffuse peritonitis without localization two cigaret drains were inserted, one in each lower quadrant. A culture of the exudate revealed E. typhosa and Escherichia coli. Succeeding cultures did not yield E. typhosa. For the next twenty-four hours a profuse purulent exudate drained from the abdominal incision, this drainage becoming less and less prominent during the succeeding days. The use of Wangensteen suction was discontinued on the third postoperative day. On the twenty-fourth day in the hospital the drains were removed and by the thirty-ninth day all drainage had ceased.

The abdominal wound continued to heal by slow granulation and peripheral epithelization, but on the fifty-third day it reopened and drained a purulent foul exudate similar to that described previously. Culture of that exudate did not yield E. typhosa. By the fifty-ninth day the drainage had ceased and the wound had healed over.

Within forty-eight hours of the initiation of surgical drainage of the peritoneal cavity, the abdomen became soft and only slightly distended. These signs persisted until the forty-fourth day, when tenderness and moderate resistance to palpation were elicited in the right lower quadrant. The tenderness and

resistance subsided with the spontaneous reopening and drainage of the surgical wound on the fifty-third day and did not recur with the subsidence of the drainage on the fifty-ninth day. Minimal herniation of the wound scar was present at the time of her discharge to the convalescent home; otherwise no abnormal abdominal signs were elicited.

Moderately severe dyspnea continued until the thirty-first day and intermittent use of oxygen was a necessity until that time. By the forty-eighth day results of physical and roentgenologic examinations of the chest were entirely normal.

Cultures of the stool were positive for E. typhosa on only the fifth and sixth days in the hospital. Cultures of blood and urine repeated throughout the illness were all negative for E. typhosa. Repeated urinalyses obtained throughout the stay in the hospital revealed no abnormalities. Representative results of blood counts selected from a total of 49 performed are shown in table 2.

TABLE 2.—*Results of Representative Blood Counts Selected from a Total of Forty-Nine*

Day in Hospital	1 P.M.*	2 A.M.	2 P.M.	3 A.M.	3 P.M.	4	5	6 to 77 (Representative [7*])
Hemoglobin concentration, Gm./100 cc.	13.5	12.0	12.5	10.0	12.0	11.5	13.0	12.0
Erythrocytes, millions/cu.mm.	4.4	3.4	3.9	3.5	3.7	4.0	3.7	3.8
Leukocytes, thousands/cu.mm.	5.2	18.4	19.5	26.0	25.4	19.3	12.0	8.1
Neutrophils, per cent	56.0	77.0	90.0	86.0	87.0	86.0	77.0	73.0
Segmented	39.0	61.0	56.0	31.0	48.0	69.0	55.0	60.0
Stab	17.0	14.0	29.0	51.0	39.0	13.0	20.0	12.0
Myelocyte	....	2.0	5.0	4.0	12.0	4.0	2.0	....
Eosinophils, per cent	....	....	....	....	....	....	....	1.0
Basophils, per cent	....	....	....	....	....	....	....	....
Lymphocytes, per cent	36.0	20.0	10.0	14.0	1.0	13.0	20.0	26.0
Monocytes, per cent	8.0	3.0	....	....	....	1.0	3.0	1.0
Toxic granules in leukocytes	++	++	++	++	+	—	—	—

*Blood transfusions given.

Approximately one to three semiliquid green-brown stools were passed daily during the first sixteen days in the hospital, and from the seventeenth to the twenty-first days no stools were passed. From the twenty-first day until the time of her discharge three large, soft brown stools were passed daily.

The temperature fluctuated between 101 and 105 F. for the first thirty-four days, and from the thirty-fifth to the forty-seventh days it varied daily from 98.6 to 105 F., spiking irregularly. From the forty-seventh through the fiftieth days it ranged from 100 to 101.4 F., and from the fiftieth through the seventy-seventh days it was within normal limits.

The pulse rate ranged from 130 to 160 and the respirations from 30 to 60 per minute until the thirty-first day in the hospital, when they began to drop to normal by lysis.

During the first seventeen hospital days the child was maintained exclusively by continuous intravenous administration of fluids, consisting of whole blood, plasma, glucose solution, protein hydrolysates (amigen®), isotonic sodium chloride solution, lactated Ringer's solution, sodium lactate solution and distilled water (averaging approximately 2,000 cc. every twenty-four hours). A vitamin B prep-

aration (solu-B®) and vitamin C were administered parenterally daily. On the seventeenth day administration of fluids by mouth was begun and on the eighteenth day a soft diet started, this being increased to a regular diet by the twenty-fourth day. From that day until the day of her discharge a diet high in calories, protein, vitamins and iron was maintained. Penicillin, 100,000 units, and streptomycin, 125,000 units, were administered intramuscularly every three hours for thirty-seven and thirty-three days, respectively. Sulfadiazine was administered orally from the twenty-fifth to the thirty-seventh days, with the blood level ranging from 8.1 to 16.8 mg. per hundred cubic centimeters.

The child weighed 38 pounds (17.2 Kg.) on the fifty-fifth day, that being only 4 pounds (1.8 Kg.) less than her weight on admission to the hospital, and when discharged she weighed forty-five pounds (20.4 Kg.).

After seventy-seven days of hospitalization, she was transferred to the country home for convalescence. At that time and four months later complete physical examinations revealed no abnormalities, with the exception of a small incisional hernia.

An intensive search by the local health department failed to disclose the source of infection.

COMMENT

Perforation of a typhoid ulcer usually occurs during the second through the fourth weeks of the disease, although in a rare case perforation may take place as early as the first week.[2] Such was the case herein reported. Perforations may be indicated by a sudden transient leukocytosis replacing a leukopenia,[1a] as reported here, but this does not always hold true. It is generally agreed that there is but one form of therapy for typhoid peritonitis, that being early surgical intervention. According to Wiley,[4] the rate of mortality due to typhoid peritonitis increases with each hour that passes after the perforations occur; hence the desirability of early surgical treatment. Although this is the general rule, operation at the time of admission on the patient described would have meant almost certain death because of her extremely critical condition.

Many forms of surgical therapy have been attempted, the most generally accepted being suture of the perforations and drainage of the most dependent parts of the wound (Hutcheson).[1a] Owing to the friability of the bowel, some cases will not lend themselves to suturing and are usually managed by placing an enterostomy tube through the point of perforation and bringing it out onto the abdominal wall for drainage (Muir and Chia).[1b] Fecal fistulas result from most surgical procedures and, fortunately, clear up spontaneously after several months in most instances.[1b] Liège and Folliasson[2] contended that cholecystostomy is preferable to cholecystectomy for perforation of the gallbladder, the former being the simpler procedure. More radical surgical treatment consists of resection of the involved portion of bowel. In most cases the abdominal exudate is seropurulent, inasmuch as the surgical procedure is performed early; hence, the perforations lend themselves to suturing. However, in the case presented the exudate was thick, purulent and plastic and it would have been impossible to find the site or sites of perforation; therefore, drainage of the abdomen was all that could be attained. One would also hesitate to handle the bowel in this case because of its friability. Muir and Chia[1b] reported that surgical treatment is often complicated by bronchopneumonia; however, in the case reported bronchopneumonia existed prior to surgical intervention and cleared

4. Wiley, R. M.: Report of a Case of Typhoid Fever, with Perforation, Virginia M. Monthly **49**:649 (Feb.) 1923.

rather than progressed following treatment. Intestinal obstruction due to adhesions may be a late complication. Scott and Ortner [5] cited a case with successive multiple intestinal perforations. The possibility of hepatic and subdiaphragmatic abscesses must be kept in mind.

In view of the common practice of immunization against typhoid it might be of interest to note that Dubrow [6] reported a case of perforation of a typhoid ulcer in a soldier who had been adequately immunized. Although this instance occurred, it is the exception rather than the rule and should in no way deter one from performing typhoid immunization procedures.

SUMMARY

An unusual case of a perforation of a typhoid ulcer masked by an attack of measles is reported. The perforation apparently occurred during the first week of the disease. Contrary to the generally accepted procedure, surgical treatment was delayed because of the patient's extremely critical condition. Complete recovery resulted.

The literature is reviewed.

2721 Connecticut Avenue.

5. Scott, E. P., and Ortner, A. B.: Typhoid—Successive Intestinal Perforations with Recovery, Am. J. Dis. Child. **68**:119 (Aug.) 1944.

6. Dubrow, A. A.: Perforation of the Intestine Due to Typhoid, J. A. M. A. **126**:495 (Oct. 21) 1944.

STIMULATION OF MANDIBULAR GROWTH IN CONGENITAL MICROGNATHIA BY TRACTION

WILLIAM P. LONGMIRE Jr., M.D.*
Professor of Surgery, University of California Medical School
LOS ANGELES
AND
MARSHALL C. SANFORD, M.D.‡
WASHINGTON, D. C.

DOUGLAS [1] presented a method of overcoming the obstructive dyspnea associated with congenital micrognathia by suture of the anterior portion of the tongue to the inner surface of the lower lip, thus bringing the base of the tongue forward out of the hypopharynx and interrupting its ball-valve action during inspiration.

Five of the 6 patients described by Douglas were fed after operation by bottle with the use of the Davis-Dunn [2] maxillary guard attachment to stimulate the development of the mandible. The subsequent growth of the lower jaw was apparently satisfactory in the 2 patients on whom follow-up reports were given.

It is the purpose of this communication to present a method of prolonged gentle traction which was successfully used to stimulate the development of the mandible in a case of severe congenital micrognathia. In this case the obstructive dyspnea had been relieved by the procedure described by Douglas but the Davis-Dunn maxillary guard attachment could not be used because the infant was unable to take nourishment from a bottle.

REPORT OF A CASE

V. A., a girl weighing 2,910 Gm., was born March 9, 1947, with pronounced underdevelopment of the mandible and a cleft of the soft palate (fig. 1). With the mouth open the tongue seemed to rest far back in the hypopharynx and only the tip and a small segment of the anterior part of the tongue could be seen. At times the tip of the tongue passed through the wide cleft in the soft palate up into the nasopharynx behind the posterior border of the hard palate. Immediately after birth she began to have repeated attacks of severe cyanosis which could be relieved only by lowering the head, using suction in the nasopharynx and stimulating the child to cry. Constant inhalation of oxygen alone was not sufficient to prevent the attacks of cyanosis. The underdevelopment of the mandible was demonstrated by roentgenograms (fig. 2). There were no other abnormalities.

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*Formerly Associate Professor of Surgery, Johns Hopkins University School of Medicine, Baltimore.

‡Formerly Assistant in Surgery, Johns Hopkins University School of Medicine, Baltimore.

1. Douglas, B.: The Treatment of Micrognathia Associated with Obstruction by a Plastic Procedure, Plast. & Reconstruct. Surg. **1**:300, 1946.

2. Davis, A. D., and Dunn, R.: Micrognathia: A Suggested Treatment for Correction in Early Infancy, Am. J. Dis. Child. **45**:799 (April) 1933.

As relief from the attacks of respiratory embarrassment seemed urgent, the operative procedure described by Douglas to advance the tongue was performed four hours after birth.

With the patient under local infiltration anesthesia induced with procaine hydrochloride, 0.5 per cent, a traction suture was placed through the anterior

Fig. 1.—Infant at birth, showing extreme micrognathia.

Fig. 2.—Roentgenogram showing underdevelopment of mandible at birth.

part of the tongue, and the mucosa of the floor of the mouth was incised around the tongue. Further blunt dissection in the floor of the mouth about the tongue permitted it to be advanced until the tip protruded beyond the lips. The tongue seemed to be of normal size. A midline incision was made in the mucosa of the under surface of the tip of the tongue and extended out over the alveolus of the mandible onto the inner surface of the lower lip. The mucosal incision in the

floor of the mouth was then closed, the tongue being advanced with each suture. Finally, the under surface of the tip of the tongue was sutured to the incision on the inner surface of the lower lip. This procedure held the tongue forward satisfactorily and respirations thereafter were adequate.

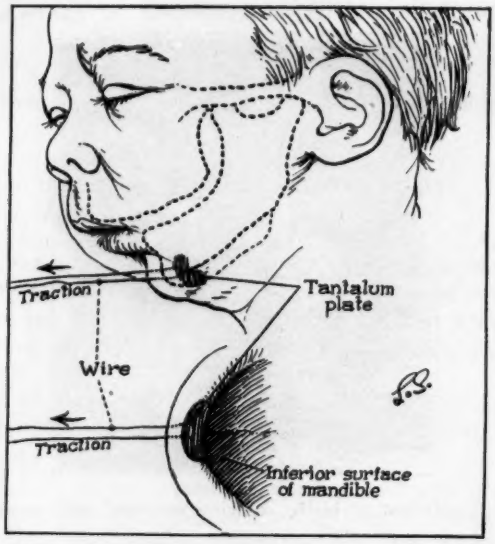

Fig. 3.—Diagram indicating position of tantalum plate and traction wire.

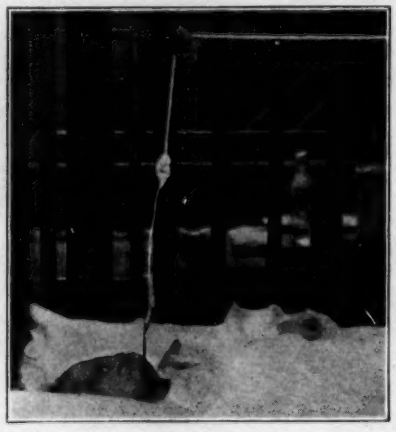

Fig. 4.—Constant traction apparatus with overhead pulley.

For the next six weeks an unsuccessful attempt was made to train the child to nurse from a bottle; however, the majority of feedings during this time had to be given by gavage. The child was able to take some nourishment from a rubber-tipped syringe but was never able to feed by bottle. It was our opinion that both the cleft in the soft palate and the attachment of the tongue of the lower lip interfered with the child's attempts to feed by nipple, as both sucking and swallowing were inadequate.

It had been planned that the maxillary guard for use with the nursing bottle described by Davis and Dunn would be used to aid in the development of the mandible, but, as the child was unable to take nourishment by the nipple, this plan had to be abandoned. It was decided to attempt to stimulate the growth of the mandible by gentle prolonged traction.

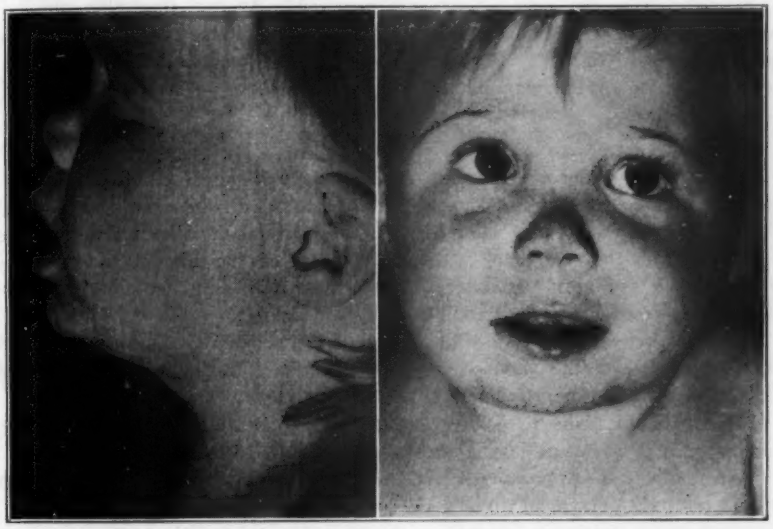

Fig. 5.—Photographs of child's face one year after birth. Left, profile view showing normal mandibular development. Right, front view of face showing normal mandibular symmetry.

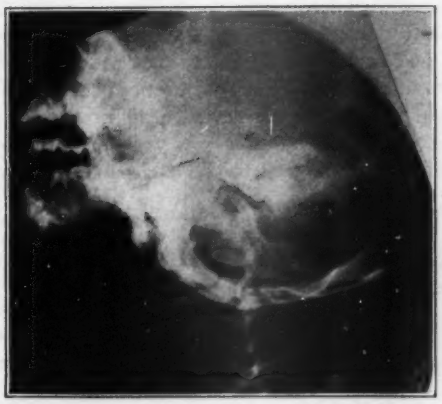

Fig. 6.—Roentgenogram of mandible made one year after birth, showing normal development.

Two months after birth a tantalum plate was inserted behind the symphysis of the mandible through a small incision beneath the chin and a tantalum wire attached to the plate brought out through the mandible and the skin (fig. 3). The wire was attached to a 15 Gm. weight through a system of pulleys arranged so as to exert a constant gentle forward pull on the mandible (fig. 4). A slight

flattening of the occipital region of the skull developed during the three month period that traction was maintained, but at the end of this period the length of the mandible seemed normal. After traction was discontinued, the tongue was released from the lip and alveolus and the child began to take nourishment by mouth. There was some regurgitation of feedings through the nose. Respirations remained satisfactory.

One year later the cleft palate was repaired. At this time the stimulated development of the mandible seemed to have been maintained and the lower jaw appeared normal (fig. 5). Roentgenograms showed a definite improvement in size and position of the mandible (fig. 6).

COMMENT

Micrognathia, if uncorrected, may be extremely disfiguring in later life, and treatment of the deformity in infancy seems indicated whenever feasible. The method recently described by Dingman [3] of the bilateral division and advancement of the body of the mandible, with preservation of the inferior dental nerve, appears to be the most satisfactory method of correcting the deformity if it has been neglected until the mandible is fully developed.

In the majority of cases of slight or moderate congenital micrognathia, bottle feedings with use of the Davis-Dunn maxillary guard during early infancy seem to promote an adequate development of the mandible.

If the mandible fails to develop under such treatment or if the situation is such that use of the maxillary guard is not feasible, as in the case described in this paper, the use of prolonged gentle traction seems to produce satisfactory results and its employment should be considered.

If obstructive dyspnea is present in the newborn infant with congenital micrognathia, it should be promptly relieved by the operative procedure described by Douglas.

SUMMARY

A case of congenital micrognathia with severe respiratory obstruction is presented. The obstructive dyspnea was adequately relieved by suturing the tongue forward to the lower lip, a procedure that was described by Douglas.

Although the maxillary guard for attachment to the nursing bottle described by Davis and Dunn to promote the development of the mandible could not be used, satisfactory growth of the lower jaw was obtained by prolonged gentle traction on a tantalum plate inserted behind the mandibular symphysis.

405 Hilgard Avenue (24) (Dr. Longmire).

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3. Dingman, R. O.: Surgical Correction of Developmental Deformities of the Mandible, Plast. & Reconstruct. Surg. **3**:124, 1948.

CHRONIC EMPHYSEMATOUS CAVITY OF THE LUNG

HERMANN VOLLMER, M.D.
NEW YORK

THIS IS a twenty-one year follow-up report on what appears to be an emphysematous cavity first observed [1] in the right lung of a 6 year old girl.

REPORT OF A CASE

In November 1926, at the age of 5½ years, this child had fever, the temperature being between 38 and 39 C. (100.4 and 102.2 F.) for twelve days, and a nonproductive cough. Thereafter, her temperature remained normal. However, she made a slow recovery, continued to cough and appeared chronically ill. A roentgenogram of the chest in March 1927 showed a dense, round infiltration in the right hilar region. Since a cutaneous tuberculin test gave a "slightly positive" reaction after twenty-four hours, the family physician diagnosed the condition as primary tuberculosis.

When I saw the child first, forty-eight hours after the cutaneous tuberculin test had been done, the skin reaction was negative. A second Pirquet test and a Mantoux test with 0.1 mg. of old tuberculin likewise produced negative reactions. The temperature of the child was always below 37 C. (98.6 F.). Her erythrocyte sedimentation rate was normal. Her blood count showed 8,000 white cells, with 4 per cent eosinophils, 6 per cent stab cells, 52 per cent segmented forms, 33 per cent lymphocytes and 5 per cent monocytes. The diagnosis of primary tuberculosis was abandoned.

The child was followed roentgenographically. In May 1927, the first signs of a cavity became visible. In June 1927, a large cavity with an air-fluid level (fig. 1) was apparent. However, the child had fully recovered, was continuously afebrile and gained weight, and results of her physical examination were normal.

The child had repeated climatotherapy. According to the roentgenograms made in January and March 1928, the cavity remained essentially unchanged. The cutaneous and intracutaneous tuberculin tests, with up to 1 mg. of old tuberculin, were repeated and again reactions were negative. The erythrocyte sedimentation rate and blood cell count were within normal limits. On the basis of these findings, I diagnosed her condition as resulting from an unspecific cavity following a chronic pulmonary infection.

During the following ten years, this girl was in good health. In 1936, she emigrated, started to work and lived under continuous strain. No roentgenogram of the chest was made during this period. She never had any expectoration and coughed for only a few days whenever she had an infection of the upper respiratory tract.

A routine roentgenogram of her chest in 1948 (fig. 2) revealed a cavity with an air-fluid level in the right lung. Her physician suspected a tuberculous cavity and, after hearing her past history, contacted me.

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1. Vollmer, H.: Cystische Lungengebilde im Kindesalter, Ztschr. f. Kinderh. **46**:810, 1928.

At this time, results of her physical examination were entirely normal. The tuberculin patch test gave a positive reaction, and her erythrocyte sedimentation rate and blood cell count were within normal limits. No sputum could be obtained

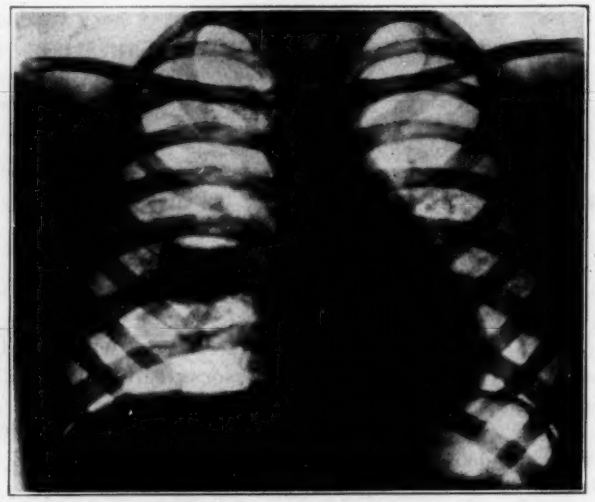

Fig. 1.—Roentgenogram made in June 1927 showing fully developed cavity with air-fluid level.

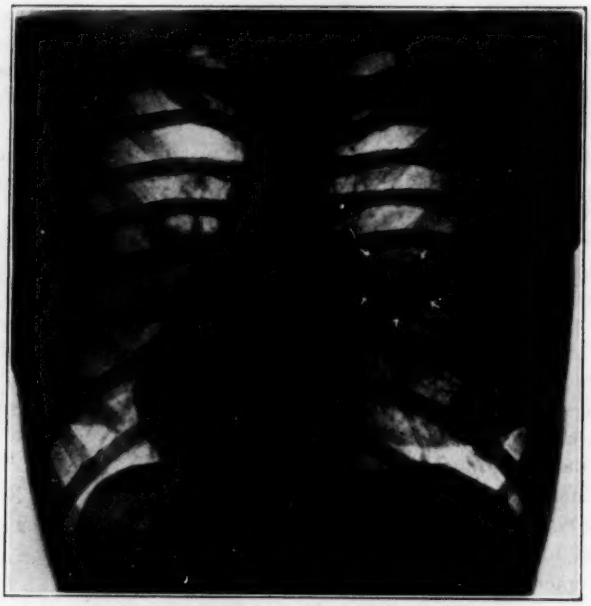

Fig. 2.—Roentgenogram made in June 1948, twenty-one years after that in figure 1, showing presence of the same cavity, unchanged in appearance.

by postural drainage. By fluoroscopy, a sharply circumscribed cyst, 33 to 39 mm. in diameter, was visible at the base of the upper lobe of the right lung, surrounded by normal pulmonary tissue. The fluid level filled about half of the

cavity and shifted with change in position. While in the previous roentgenograms, twenty-one years before, the cavity had approximated half the hemithoracic diameter, it was now only about one third of this diameter. Obviously, the cyst had not grown at the same rate as the chest.

COMMENT

On the basis of the available data, the nature of this cavity cannot be determined with certainty but with a high degree of probability, through exclusion of causes which may lead to similar roentgenographic phenomena.

A congenital cyst can be ruled out since the child was asymptomatic to the age of 5½ years, and a routine fluoroscopy at the age of about 4 years had shown normal lungs.

A tuberculous nature of the cavity can be excluded by the repeated negative cutaneous reactions, the normal sedimentation rates, the normal blood cell counts and the absence of constitutional symptoms over a period of twenty-one years. Though the tuberculin patch reaction is now positive, this result must be ascribed to an infection occurring years after the cavity had developed.

Pulmonary abscess, though consistent with the roentgenographic findings in this case, is highly improbable. Such lesions occur rarely beyond infancy and are usually multiple and accompanied with constitutional symptoms and leukocytosis. The long duration without any essential change and the asymptomatic course in this case exclude the presence of a pulmonary abscess with a fair degree of certainty.

Fluoroscopic examination showed the cavity surrounded by pulmonary tissue and, therefore, not situated in the pleural space. Consequently, a loculated pneumothorax can be ruled out.

Echinococcus cysts are rare in childhood, show a different roentgenographic appearance,[2] change in size and have a poor prognosis. Lack of eosinophilia and the negative cutaneous reactions in this case are additional evidence against echinococcus.

Thus, differential diagnostic considerations leave as the most acceptable interpretation of this case an emphysematous cavity distal to a bronchial obstruction of the check-valve type, which was caused by a pulmonary infection.

Such cases seem not to be as infrequent as was formerly stated. Benjamin and Childe,[3] as well as Caffey,[4] encountered 39 emphysematous cysts. Caffey gave a comprehensive clinical and roentgenographic description and a complete review of the pertinent literature. All these cases were associated with or followed a respiratory infection, ran an asymptomatic course and finally cleared up spontaneously. All data here presented are consistent with the diagnosis of an emphysematous cavity. Exceptional are the follow-up period of twenty-one years and the long duration of the lesion. For these I can offer no convincing explanation. Several diagnostic procedures, such as a bronchoscopy, could have contributed to a clearer determination and understanding of this case. Since they are potentially dangerous, they were not performed nor could they be recommended.

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2. Behrenroth, E.: Beiträge zur Klinik des Lungenechinokokkus, Deutsches Arch. f. klin. Med. **107**:480, 1912.

3. Benjamin, B., and Childe, A. E.: Localized Bullous Emphysema Associated with Pneumonia in Children, J. Pediat. **15**:621, 1939.

4. Caffey, J.: Regional Obstructive Pulmonary Emphysema in Infants and in Children, Am. J. Dis. Child. **60**:586 (Sept.) 1940.

SUMMARY

A pulmonary cyst is described which was first observed in a 6 year old girl following a pulmonary infection. Reexamination twenty-one years later revealed that this cavity had persisted without essential change in size and roentgenographic appearance. The course was asymptomatic. Differential diagnostic considerations made an emphysematous cavity the most probable diagnosis. The case of this patient was one of the first described in the literature and has the longest follow-up period. It teaches that not all emphysematous cavities disappear spontaneously and that, nevertheless, a conservative attitude is to be recommended.

Dr. John Caffey interpreted the existing series of roentgenograms in this case, and Dr. Kurt Jellinek contributed the roentgenogram of figure 2.

25 Central Park West.

PHENYLPYRUVIC OLIGOPHRENIA

Two Cases of Siblings

ROBERT ORR WARTHEN, M.D.

MORRIS TANDETA, M.D.

AND

JONATHAN M. WILLIAMS, M.D.

WASHINGTON, D. C.

PHENYLPYRUVIC oligophrenia (imbecillitas phenylpyruvica) was first described by Følling [1] in 1934. Since that time, reports of approximately 300 cases have appeared in the literature, the majority of these cases having been recorded by Jervis.[2] Dann and his associates [3] reported an incidence of 0.8 per cent among institutionalized feebleminded persons. Holt and Howland [4] estimated that patients with phenylpyruvic oligophrenia comprise 1 to 2 per cent of all mentally defective persons. Medlicott [5] found 2 cases among 190 mentally defective persons examined (an incidence of 1.1 per cent).

This malady is characterized by severe mental deficiency, neurologic manifestations and the abnormal finding of phenylpyruvic acid in the urine. Most patients exhibit definite physical features [6]; i. e., they are usually well developed, obese, attractive persons with blond hair, a fair complexion and blue eyes. The mental retardation is generally more pronounced than that accompanying mongolism and other types of mental deficiency,[6] Ford [7] reporting that 70 per cent are

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From the Children's Hospital.

1. Følling, A.: Ueber Ausscheidung von Phenylbrenztraubensäure in der Harn als Stoffwechselanomalie in Verbindung mit Imbezillität, Ztschr. f. physiol. Chem. **227**:169, 1934.

2. Jervis, G. A.: The Genetics of Phenylpyruvic Oligophrenia (Contribution to Study of Influence of Heredity on Mental Defect), J. Ment. Sc. **85**:719 (July) 1939.

3. Dann, M.; Marples, E., and Levine, S. J.: Phenylpyruvic Oligophrenia: Report of a Case in an Infant with Quantitative Chemical Studies of the Urine, J. Clin. Investigation **22**:87 (Jan.) 1943.

4. Holt, L. E., and Howland, J.: Holt's Diseases of Infancy and Childhood, revised by L. E. Holt, Jr. and R. McIntosh, ed. 11, New York, D. Appleton-Century Co., Inc., 1940, pp. 1012 and 1348.

5. Medlicott, R. W.: Some Rarer Forms of Mental Deficiency: I. Phenylpyruvic Oligophrenia, New Zealand M. J. **43**:191 (Aug.) 1944.

6. (*a*) Dann and others.[3] (*b*) Himwich, H. E., and Frazekas, J. F.: Cerebral Metabolism in Mongolian Idiocy and Phenylpyruvic Oligophrenia, Arch. Neurol. & Psychiat. **44**:1213 (Dec.) 1940. (*c*) Penrose, L. S.: Two Cases of Phenylpyruvic Amentia, Lancet **1**:23 (Jan. 5) 1935.

7. Ford, F. R.: Diseases of the Nervous System in Infancy, Childhood and Adolescence, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1944, pp. 253 and 254.

imbeciles and 30 per cent idiots, and Jervis [2] reporting about 35 per cent imbeciles and 65 per cent idiots. Clumsiness, repetitive movements, restlessness and distractibility are common among these patients just as they are among other mentally defective persons. The motor activities are usually slow and the patients are easily managed. Growth and development generally follow or are somewhat behind those of other mentally retarded persons. In childhood the posture varies from normal to a flexion position with the body maintained rigidly forward. The neurologic symptoms and signs involved are related to the motor or extrapyramidal tracts.[8] Among the common observations are muscular rigidity and hypertonicity, hyperactive deep tendon reflexes, knee and ankle clonus, tremors, choreiform or athetotic movements and occasional convulsive seizures. The spinal fluid is uniformly normal, and pneumoencephalography occasionally discloses slight dilatation of the ventricles and sulci.[7]

The following case reports are of 2 siblings afflicted with phenylpyruvic oligophrenia.

REPORT OF CASES

CASE 1.—C. B., a 20 month old white female infant, was admitted to Children's Hospital for evaluation of a mentally retarded state which had been observed since the age of 8 months. At that time she had failed to sit up, turn over in bed or play with toys as expected. She was unable to focus her eyes, push herself up on her arms when lying prone or hold a bottle. She was easily startled by loud noises, responded to the approach of her mother at times by laughing and cooing and was adept at putting small objects in her mouth. The first teeth appeared between 8 and 9 months of age. The past history revealed this infant to be a premature infant of seven months' gestation. She was delivered rather precipitously after one hour's labor. The mother had had episodes of false labor occurring one month and two weeks prior to delivery. The weight at birth was 5 pounds 2 ounces (2,324 Gm.) and no neonatal complications were noted. The medical history was otherwise noncontributory.

Physical examination revealed a well nourished, white blond female infant lying on her back with outstretched extremities. No evidence of disease was apparent, with the exception of hypertrophied tonsils. Exotropia was evident and the fundi were normal. The important signs were developmental:

Motor Behavior: She was able to sit with support, held her head erect, was unable to turn completely over, had difficulty in swallowing solids and drinking liquids from a bottle, and was hypotonic.

Adaptive Behavior: She smiled when approached and regarded the face of the examiner, followed a bright light and withdrew on painful stimulation.

Language and Social Behavior: She cooed, smiled and seemed to enjoy being pulled up and regarded her hands pleasurably.

The developmental progress was estimated at about 16 weeks (Gesell developmental quotient of 20). The blood serologic reaction was negative. Phenylpyruvic acid was present in the urine.

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8. Jervis.[2] Jervis, G. A.: Phenylpyruvic Oligophrenia: Introductory Study of Fifty Cases of Mental Deficiency Associated with Excretion of Phenylpyruvic Acid, Arch. Neurol. & Psychiat. **38**:944 (Nov.) 1937.

CASE 2.—J. B., the 9 month old brother of C. B., was also admitted to the hospital for evaluation of mental retardation. At the age of 4 months he was thought to be blind because of failure to follow objects with his aimlessly wandering eyes. He was easily startled by loud noises. Past history revealed that he, too, had been born prematurely at seven months' gestation after one hour's labor. His weight at birth was 5 pounds 7½ ounces (2,480.6 Gm.). There were no illnesses during the pregnancy. The infant's weight dropped to 4 pounds 11 ounces (2,126.2 Gm.) almost immediately after birth and he was maintained on fluids given parenterally throughout his eight days of hospitalization; otherwise, he seemed to progress satisfactorily. There were no convulsive seizures.

Physical examination on his admission revealed a white blond male infant lying on his back and appearing rather irritable. The tonsils were hypertrophied; the pupils reacted sluggishly to light, and exotropia was evident. The fundi were normal. Developmental observations were as follows:

Motor Behavior: He sat erect only with support and was unable to hold his head erect or to raise it while lying in the prone position.

Adaptive Behavior: He gave no response to visual stimulation.

Social and Language Behavior: His features were impassive except when he was crying.

His developmental progress was estimated at 8 weeks (Gesell developmental quotient of 20 to 25). Phenylpyruvic acid was present in the urine and the blood serologic reaction was negative.

The parents were of French Canadian and German descent. There was no knowledge of mental retardation, nervous disease or consanguinity in any relatives, nor were there other familial diseases. Neither the mother nor the father had phenylpyruvic acid in the urine.

COMMENT

Jervis[2] in an extremely exhaustive study of 200 patients with phenylpyruvic oligophrenia and their families showed that the developmental defect is determined by a single autosomal recessive gene. In his series there was a familial incidence of 68 per cent. It is also of interest that the rate of consanguinity among parents of affected persons is significantly higher than that of normal persons.[8]

This syndrome of a particular type of mental deficiency, coupled with the abnormal finding of phenylpyruvic acid in the urine as the result of incomplete oxidation of the essential amino acid phenylalanine,[9] is probably due to two primary developmental defects. The mental and neurologic manifestations are probably the expression of a cerebral developmental defect, whereas the incomplete metabolism of phenylalanine probably represents a biochemical developmental defect.[8] It is of interest to note that phenylpyruvic acid has never been demonstrated in the urine of a normal person.

In view of the fact that this condition is transmitted by a single recessive gene, it becomes mandatory that the parents of children with the disorder be discouraged from having more children. Parenthood should also be denied those afflicted with the disease, as well as their brothers, sisters, uncles and aunts.[2]

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9. Penrose.[6e] Ford.[8] Phenylpyruvic Oligophrenia, Current Comment, J. A. M. A. **112**:1729 (April 29) 1939.

SUMMARY

Phenylpyruvic oligophrenia is a relatively rare condition characterized by pronounced mental retardation, neurologic manifestations and the abnormal finding of phenylpyruvic acid in the urine.

The mental and neurologic, as well as the biochemical, defects are apparently determined by a single recessive gene.

Parents of persons with the condition should be discouraged from having more children. Parenthood should be denied those afflicted with the disease, as well as their immediate relatives.

Two cases of phenylpyruvic oligophrenia in siblings are reported.

The literature is reviewed.

2721 Connecticut Avenue.

Progress in Pediatrics

THE NATURE OF INFANTILE CONVULSIONS

ROBERT A. SHANKS, M.D., M.R.C.P., F.R.F.P.S.
GLASGOW, SCOTLAND

CONVULSIONS in infants and young children have been known and feared since medicine began, but it is only in comparatively recent years that a systematic study of their causation has been made. By the end of the ninteenth century, Hughlings Jackson and Soltmann had already made their contributions and rather earlier Clarke had described convulsions associated with carpopedal spasm and laryngismus.[1] Thus there had already been an attempt to separate from the main group of infantile convulsions those which might properly be called epileptic, while the convulsions of tetany were also recognized. The researches of Soltmann led him to postulate an immature nervous system which was, therefore, hyperirritable to peripheral stimuli. This explanation of the hypersusceptibility of infants to convulsions fell on ready ears. It was a poor physician indeed who could not find some cause of peripheral irritation in a convulsing child, although none, presumably, felt constrained to warn the mother of the imminence of a fit when her child had worms or indigestion.

This then was the position at the beginning of the twentieth century, and, when one surveys the more recent literature, there are still discernible three more or less distinct preoccupations. Some writers maintain that there is a fundamental unity in all convulsions, whatever the ostensible cause. Others recognize only two groups in the classification of convulsions, one, epileptic, and the other, symptomatic; those of the latter group may be "symptomatic" of such varied conditions as tetany, uremia and intracranial disease. Others again recognize in addition a specific "casual" convulsion distinct from both epilepsy and tetany.

This concept of a benign nonrecurrent convulsion occurring at the onset of an illness in infants and young children and unrelated to either tetany or epilepsy is one that gained a large degree of support, especially in Germany. It was first formulated in 1905 by Hochsinger,[2] and the

From the Department of Child Health, University of Glasgow, and the Royal Hospital for Sick Children.

1. Shanks, R. A.: The Historical Background of Convulsions in Childhood, Arch. Dis. Childhood **23**:281, 1948.

2. Hochsinger, K.: Krämpfe bei Kindern, Deutsche Klin. **2**:479, 1905.

idea is, of course, a lineal descendant of Soltmann's theory of peripheral hyperirritability. These convulsions have gone by many names. Hochsinger called them "casual" convulsions (*Gelegenheitskrämpfe*), but they have also been called "initial fever convulsions," "fever convulsions" and "incidental convulsions." The disturbance of health that was regarded as adequate to cause such a convulsion varied with different authorities. Some would accept only the convulsions that ushered in acute febrile illnesses as belonging to the "casual" class. Others were of the opinion that teething, colic and the whole gamut of causes of peripheral irritation would produce these convulsions, and indeed these authors differed little from their colleagues of a hundred years before.

I have elsewhere discussed the place of tetany or hypocalcemia among the causes of infantile convulsions.[3] There seems little doubt that hypocalcemia played a greater part in the causation of these convulsions than was manifest by the incidence of frank tetany. The degree to which infantile convulsions could properly be regarded as hypocalcemic must have varied from place to place and from time to time dependent on the incidence of vitamin D deficiency.

It is the relationship of infantile convulsions to epilepsy that has been the main concern of writers in the present century. In this regard it is important, I think, to realize that the term "epilepsy" is used differently by different authors. Those who discuss the prognosis of infantile convulsions and seek to differentiate between infantile convulsions and epilepsy use the term in its usual connotation of a chronic convulsive disorder often with the sequela of progressive mental deterioration. The diagnosis of epilepsy in this sense spells tragedy for the parents and the term is not lightly used by the humane physician. It is obvious from the context that this is by no means what other writers intend. Authors who maintain the unity of all convulsive disorders do not imply this unhappy prognosis in every case of convulsions but, on the contrary, inveigh against needless gloom in dealing with epi-epilepsy. Manifestly, this is a matter of definition. Those who hold that the basis of all convulsions is epileptic merely maintain that there is a fundamental unity in all convulsions however provoked and that the spontaneous recurrent convulsions, to which the term epilepsy is usually restricted, show a difference—great though it may be—which is in degree and not of kind. Thus, the term "symptomatic epilepsy" differs in no way from the term "symptomatic convulsion."

Much has been written on the subject of the prognosis of infantile convulsions, and, whatever one's views may be on the causation, the same problem presents. What is the likelihood of recurrence in a

3. Shanks, R. A.: The Changing Incidence of Convulsion in Childhood, Arch. Dis. Childhood **24**:208 (Sept.) 1949.

particular patient and what is the likelihood of ultimate mental deficiency? Here again there has been little unanimity, but it is possible without an exhaustive review of the papers in question to outline the consensus of opinion. It seems that approximately 12 per cent of infantile convulsions are followed by recurrence and probable mental degeneration. Moreover, this result is the more likely the more fits the child has or the less obvious the associated disturbance of health. The most innocent fit is the single convulsion occurring at the onset of an acute infection in a child with no previous history of convulsions and with no history of epilepsy in his immediate family.[4]

The main protagonists of the unity of all convulsions are Collier [5] and Kennedy.[6] Collier epitomizes the problem thus:

> I shall attempt the argument that the clinical phenomena met with in idiopathic epilepsy, in epilepsy from local lesions of the brain, and in the symptomatic epilepsy occurring in disordered metabolic states, in general diseases and intoxications, are identical and truly indistinguishable. And that those occurring in narcolepsy, migraine, vasovagal attacks, idiopathic syncopal attacks, and perhaps also in tetany are phenomena of the same order and are closely allied to those of epilepsy with which they occasionally mix.

Kennedy emphasized "a qualitative unity and a quantitative difference in the various manifestations of epilepsy." He went further and included not only all unequivocal convulsions in his "spectrum of epilepsy" but also the chorea of pregnancy and some cases of major hysteria. I am concerned here only with the convulsions of infancy and childhood and the problem of epileptic equivalents and psychomotor attacks need not be considered, but nevertheless, as I hope to show, this concept of a fundamental unity in convulsive seizures will be the most valuable in the elucidation of the problem.

Hughlings Jackson's postulate of a paroxysmal nervous discharge in epilepsy has received striking confirmation in electroencephalography. Without personal experience in this method one cannot pretend to assess its place in the study of convulsions, but a brief résumé of the position will be helpful to the argument. An abnormal electroencephalogram has been obtained in 85 per cent of patients whose conditions were diagnosed clinically as epilepsy, while 15 per cent of apparently normal controls showed abnormal electroencephalographic tracings. If how-

4. Patrick, H. T., and Levy, D. M.: Early Convulsions in Epileptics and in Others, J. A. M. A. **82**:375 (Feb. 2) 1924. Thom, D. A.: The Relation Between Infantile Convulsions and the Chronic Convulsive Disorders of Later Life, Arch. Neurol. & Psychiat. **11**:664 (June) 1924; Infantile Convulsions: Their Frequency and Importance, Am. J. Psychiat. **6**:613, 1924; Convulsions of Early Life and Their Relation to Chronic Convulsive Disorders and Mental Defect, ibid. **98**:574, 1942.

5. Collier, J.: Lumleian Lectures on Epilepsy, Lancet, **1**:587, 1928.

6. Kennedy, F.: On the Nature of Fits, in Epilepsy and the Convulsive State, A. Research Nerv. & Ment. Dis., Proc. (1929) **7**:30, 1931.

ever, the apparently normal controls were taken from the near relatives of epileptic persons, an abnormality was detected in approximately half the tracings. A similar proportion of abnormal tracings was found in recruits with a history of infantile convulsions. Peterman [7] maintains that an abnormal electroencephalogram always indicates a "potential epileptic" even though there has never been a recognizable fit. In practice the electroencephalogram is of value in only half the patients with a history of seizures and is perhaps of more value in those with

TABLE 1.—*Diseases Associated with Convulsions*

	1922 to 1926		1932 to 1936		1942 to 1946	
	Actual Figures	% Total	Actual Figures	% Total	Actual Figures	% Total
I. Primary Disease of the Central Nervous System						
Epilepsy	50	11.0	58	15.2	60	15.4
Inflammatory disease	121	26.6	50	13.1	46	11.8
Cerebral hemorrhage	2	0.4	17	4.4	9	2.3
Mental deficiency	27	5.9	26	6.8	53	13.6
Miscellaneous	6	1.3	4	1.1	8	2.1
Total	206	45.2	155	40.6	176	45.2
II. Without Evidence of Primary Disease of the Central Nervous System						
Respiratory system						
Acute respiratory disease	131	28.8	83	21.8	96	24.7
Infectious fevers	3	0.7	6	1.6	7	1.8
Miscellaneous	1	0.2	..	....	3	0.8
Total	135	29.7	89	23.4	106	27.2
Alimentary system						
Acute infections	22	4.8	46	12.0	36	9.3
Miscellaneous	2	0.4	2	0.5	3	0.8
Total	24	5.2	48	12.5	39	10.1
Urinary tract						
Miscellaneous	12	2.6	26	6.8	8	2.1
Miscellaneous						
Convulsions of unknown causation	44	9.7	54	14.1	48	12.3
Tetany (without infection)	17	3.7	8	2.1	7	1.8
Unclassified	16	3.9	2	0.5	5	1.3
Total	77	17.3	64	16.7	60	13.4
Total	248	54.8	227	59.4	213	54.8
Total all cases	454	....	382	....	389	....
Total admissions	5,706	....	3,769	....	4,884	....
Convulsions as percentage of total admissions	...	7.9	...	10.1	...	7.9

petit mal. It must be recognized, moreover, that disturbing inconsistencies have been reported in repeated records from the same person.[8] The relevance to infantile convulsions is restricted by the fact that, as with so many methods requiring the cooperation of the patient, the results in children have been unsatisfactory. One point of interest does, however, arise, namely, that, whereas only 12 per cent of infants with convulsions are said to have chronic convulsive disorders, 50 per cent of them show an abnormal electroencephalogram in adult life.

7. Peterman, M. G.: Convulsions in Childhood, Illinois M. J. **84**:306, 1943.

8. Nattrass, F. J.: Clinical and Social Problems of Epilepsy, Brit. M. J. **1**:1, 1949.

One can probably conclude, therefore, that in these persons there is a much higher incidence of that abnormal paroxysmal nervous discharge of which a convulsion is the occasional manifestation.

DISEASES ASSOCIATED WITH CONVULSIONS

Convulsions in childhood arise in association with a variety of diseases. They also arise spontaneously without any obvious precipitating factor. Table 1 shows the diagnoses in children with convulsions admitted to the Royal Hospital for Sick Children, Yorkhill, Glasgow, during three representative quinquennia of the quarter century of 1922 to 1946. The diagnosis for each child is the principal one in relation to the convulsion. A known epileptic child is classed as epileptic whether or not he has an acute infection. Most children with tetany, either clinical or biochemical, are included under the almost invariably associated acute infection; only in those children in whom there is no evidence of such an infection is the condition classed as tetany. This table is important in that it surveys the position over a period which has seen great changes in the pattern of medicine. Some of the changes reflect merely administrative differences. It is likely, for example, that the fall in the incidence of inflammatory disease of the central nervous system indicates only that meningococcic meningitis is no longer treated in general wards.

Obvious epilepsy forms a comparatively small part of the whole picture, and indeed less than half the cases are attributable to primary disease of the central nervous system. Of other causes those associated with acute respiratory disease form the largest single group. There is, nevertheless, a notable divergence between these figures and those published by Herlitz.[9] Herlitz, who excluded intracranial disease and considered only those cases of convulsions that were associated with an acute infection, reported 80 per cent of his series associated with acute pharyngitis. I have not made the differentiation between infections of the upper respiratory tract and pulmonary infections, to say nothing of the minute distinction between acute pharyngitis and inflammation in other sites of the upper respiratory tract. Among those cases classed as due to acute respiratory disease there was a fair proportion of instances of bronchopneumonia and acute bronchitis. Table 2 shows how only once (1922 to 1926) does the total for acute respiratory disease reach Herlitz' figure for acute pharyngitis alone. In Glasgow at least, the diseases associated with convulsions have occurred in much the same proportion as their general incidence would suggest.

It was only seldom that a precise diagnosis could not be made. These cases of "convulsions of unknown causation" might formerly

9. Herlitz, C. W.: Die sog. initialen Fieberkrämpfe bei Kindern, Acta pædiat. (supp. 1) **29**:1, 1941.

have been called "teething fits" or attributed to the varied stimuli postulated by the proponents of Soltmann's theory of peripheral hyperexcitability. In point of fact they might also have been the first epileptic fit or a missed hypocalcemic convulsion. In any event, they were never more than 14.1 per cent of the total. In a much smaller series of my own, of 64 consecutive cases of children admitted over a period of twelve months, only 3 (4.7 per cent) were so classified and even these could have been included as probably epileptic. In short, convulsions in childhood that are not associated with obvious intracranial mischief are accompanied with evident disease in by far the majority of cases and this disease is most usually an acute infection. Colic, indigestion, foreign bodies, worms and tight "woollies" play no part whatsoever.

THE POSITION OF TETANY

In a discussion of the position of tetany or, to be more precise, of hypocalcemia in the causation of infantile convulsions published else-

TABLE 2.—*Site of Infection Associated with Convulsions (Excluding Intracranial Disease)*

Site of Infection	1922 to 1926	1932 to 1936	1942 to 1946
Respiratory tract	131 (84%)	83 (62%)	96 (69%)
Alimentary tract	22	46	36
Infectious diseases	3	6	7
Total	156	135	139

where [3] it was evident that in Glasgow, at least, hypocalcemia was the predominant etiologic factor in convulsions in children under the age of 3 years until the beginning of the present decade. With the dramatic fall in the incidence of rickets that accompanied the increased physical well-being of people in this country, hypocalcemia ceased to be a factor of importance. To confirm this point, the blood chemistry was investigated in children with convulsions admitted over a twelve month period (1947-1948) and the results are given in table 3. There was only 1 child with frank tetany (case 37) and in only one other was the serum calcium level under 8 mg. per hundred cubic centimeters.

Graham [10] had already postulated hypocalcemia as the predominant cause of infantile convulsions. This led him to suggest an ingenious explanation for the initial fever convulsion.[11] Tetany, and more particularly latent tetany, is a metabolic upset which is more or less confined to members of the age group with maximum incidence of convulsions and which in itself predisposes to convulsions. Tetany would

10. Graham, S. G.: Convulsions in Infancy, Glasgow M. J. **117**:113, 1932; The Aetiology of Convulsions in Infancy, Acta pædiat. **16**:572, 1933.

11. Graham, S. G.: Personal communication to the author.

explain not only the convulsions of infancy but also their cessation. It is known that neuromuscular excitability is dependent on the amount of ionized calcium in the circulating blood and that this in turn depends, other things being equal, on the acid-base balance. Thus, an alkalemia will depress ionization and render the neuromusculature more excitable, while an acidemia will do the opposite. Obviously then, an alkalemia would convert latent tetany in which the ionized calcium is just sufficient to meet requirements, and no more, into frank tetany in

TABLE 3.—*Serum Calcium and Plasma Inorganic Phosphorus Levels in Children with Convulsions Admitted During the Twelve Month Period, August 1947 to July 1948*

Convulsions Not Attributed to Primary Disease of the Central Nervous System			Convulsions Attributed to Primary Disease of the Central Nervous System		
Case No.*	Calcium, Mg./100 Cc.	Phosphorus, Mg./100 Cc.	Case No.†	Calcium, Mg./100 Cc.	Phosphorus, Mg./100 Cc.
1	10.3	4.5	3	10.0	4.6
11	10.1	4.3	5	11.4	4.5
13	7.0	3.5	9	10.2	3.7
15	10.1	11.1‡	10	9.8	5.1
16	11.0	4.0	12	12.3	4.7
17	9.5	3.0	14	8.3	3.9
19	9.9	4.0	21	9.9	4.2
22	9.6	2.5	24	10.0	3.0
23	8.5	9.7‡	29	10.0	4.2
25	9.8	4.5	30	10.2	4.2
26	10.4	3.5	32	9.9	3.7
27	9.9	3.4	35	11.5	3.3
28	10.2	4.0	36	9.1	4.6
31	9.6	4.0	38	10.6	3.8
37	5.1	10.0‡	39	10.7	5.4
42	10.0	6.4	41	9.8	4.5
45	11.3	3.2	43	10.0	3.3
46	9.4	3.4	47	10.2	4.4
52	9.4	8.0	48	9.4	3.5
54	10.0	3.4	49	9.7	1.9
58	10.3	4.2	50	9.3	3.7
60	9.8	3.4	55	10.7	3.4
61	10.1	3.1	64	14.5	5.5
62	10.1	3.2			
63	9.9	3.6			

* No estimations were carried out for 7 patients (cases 2, 4, 7, 8, 33, 40 and 56) all of whom had terminal convulsions.

† No estimations were performed for 9 patients (cases 6, 18, 20, 34, 44, 51, 53, 57 and 59). Four of these patients had terminal convulsions only.

‡Calculations were made while child was at the point of death.

which the ionized calcium is inadequate to restrain the neuromuscular excitability. There is abundant evidence that the onset of pyrexia, whether produced artificially or in disease, is accompanied with a temporary alkalemia.[12] This is, of course, only temporary and increased

12. Hill, L., and Flack, M.: The Influence of Hot Baths on the Pulse Frequency, Blood Pressure, Body Temperature, Breathing Volume and Alveolar Tensions of Man, J. Physiol. **38**:lvii, 1909. Bazett, H. C., and Haldane, J. B. S.: Some Effects of Hot Baths on Man, ibid. **55**:iv, 1921. Koehler, A. E.: Acid-Base Equilibrium, Clinical Studies in Alkalosis, Arch. Int. Med. **31**:590 (April) 1923. White, A. C.: The Bicarbonate Reserve and the Dissociation Curve of Oxyhaemoglobin in Febrile Conditions, J. Exper. Med. **41**:315, 1925. Hartmann, A. F., in discussion on Acidosis and Alkalosis, Pediatrics **2**:584, 1948.

catabolism produces an overcompensation thereafter. A temporary change, however, is all that would be required to initiate a convulsion at the beginning of an infection in a child whose ionic calcium equilibrium was precarious. Latent tetany, in which there might well be no signs (especially after a fit) and in which the total serum calcium might not be significantly lowered, was a perfectly reasonable suggestion for the causation of infantile convulsions during the period that frank tetany and rickets were not uncommon. Recent American work from Japan, where nutritional deficiencies are widespread, has shown a rather similar position. In the disease ekiri there is demonstrated the relation between fever, a respiratory alkalosis and the convulsions of tetany.[13] Now that neither rickets nor frank tetany is met with except on rare and exceptional occasions such factors seldom operate and hypercalcemia in infantile convulsions must be regarded as a rarity.

THE CONSTANT INCIDENCE

One recognizes that factors other than the incidence of the disease concerned are reflected in the numbers admitted to a hospital. When, however, the condition is acute and one with which the child will usually be admitted to hospital, and when the hospital is one that can be assumed to take most of the children with acute disease in its area, there will be a fair correspondence between the numbers of admissions and the actual incidence of the particular condition in the area. One can correct for the variable turnover of admissions by expressing the figures as a percentage of the total admissions. It is then obvious that, in spite of the virtual disappearance of what used to be a major etiologic factor, there has been no change in the total incidence of convulsions. Children with convulsions were 7.9 per cent of the total admissions in 1922 to 1926 and 7.9 per cent again in 1942 to 1946. What is more important, the relative proportions in the various subgroups in table 1 show little variation. The same proportions, more or less, are associated with acute respiratory disease in 1922 to 1926 (28.8 per cent), when a large number of the children were demonstrably hypocalcemic, as there are in 1942 to 1946 (24.7 per cent), when hypocalcemia was rare. This constant pattern of incidence in the face of the virtual disappearance of a major etiologic factor is an observation of some importance in understanding the problem of infantile convulsions.

COMMENT

When the changing views of physicians through the ages are considered, it is obvious that there has been a constant struggle to relate every convulsive seizure to an obvious and immediate cause. It seemed

13. Dodd, K.; Buddingh, G. J., and Rapoport, S.: The Etiology of Ekiri: A Highly Fatal Disease of Japanese Children, Pediatrics **3**:9, 1949.

manifestly impossible that there should not be a multitude of causes for a condition that occurred in such differing circumstances. Convulsions did not attract attention simply because of the alarming nature of the attacks, for they might on that account have been relegated to the position of an alarming symptom such as delirium. This condition which could initiate an acute illness or terminate the scene could also arise spontaneously with no apparent illness before or after the fit. Furthermore, these seizures bore no relation whatever to the degree of illness. Accordingly, more and more causes were adduced and yet none of them, not even organic disease of the brain, was invariable in its effect. In this connection Crump [14] has made the interesting observations that only little more than half of those with meningitis have convulsions and even in frank tetany some 10 per cent escape. There arose not unnaturally, therefore, a tendency to regard almost any preceding event as an etiologic factor, and for this reason it is not surprising that teething should have been regarded as a potent cause. Almost any child from the age of 6 to 18 months is either teething or about to be teething, and this age group was prominent in infantile convulsions in the past. With the fall in the incidence of hypocalcemic convulsions, however, the main incidence has changed to the first three months of life.[8]

If a large number of factors, all differing in kind and degree, can sometimes but not always produce a convulsion, only a limited causal relationship can be attributed to these various factors and they can at best be only proximate causes. This led to the twentieth century view of the hyperexcitability of the infantile nervous system which was never satisfactory. This view premised that the child had a convulsion by virtue of his youth rather than by virtue of an individual and inherent tendency. The former opinion is unsatisfactory in that only few children have convulsions, while they are, after all, all young; furthermore, there is no correlation between the degree of provocation and the appearance of a fit. Certainly, the most striking examples of peripheral irritation, such as burns, are only rarely accompanied with convulsions, while the most trivial and commonplace of peripheral stimuli had often to suffice as the cause of a major fit.

Against the theory that all infantile convulsions are the result of an innate proclivity is the objection that most of these children have no more convulsions. If one accepts as a conservative estimate that about 12 per cent of infants with convulsions have recurrences, it means, of course, that 88 per cent have no more fits. The fate of this convulsive tendency in the latter group must then be considered. As

14. Crump, E. P.: Convulsions in Infants and Children, Journal-Lancet **65**:182, 1945.

previously mentioned, an abnormal electroencephalogram was observed in half of them suggesting a latent convulsive state and they might, therefore, be called "potential epileptics." For the rest the necessity of postulating a fundamental difference between those with normal and those with abnormal electroencephalograms is not certain; it is known, for example, that some who have recurrent spontaneous convulsions have, nevertheless, no demonstrable abnormality in the electroencephalographic tracing. It may well be that, whereas a person has convulsions primarily because of an inherent proclivity, when and how often he has them depends on other, possibly environmental, factors. The discovery of tetany and, more particularly, latent tetany appeared at first to be the solution, although the skeptic will note that not all children with tetany had convulsions, even in the presence of an acute infection. In any case, it is now no longer possible to attribute the majority of infantile convulsions to hypocalcemia. Furthermore, it has already been pointed out that there has been no reduction in their incidence. One is, therefore, forced to one of two conclusions—one, that the fall in hypocalcemic convulsions has been compensated for by a fortuitous rise in the incidence of another and unknown etiologic factor, and the other, which is the one that I would tentatively submit, that hypocalcemia was never the real cause of convulsions but only a precipitating factor. Thus, the spasmophilic diathesis merely determined the seasonal and age distribution without affecting the total incidence. I would submit that no cause yet cited can be satisfactorily regarded as anything more than a precipitating factor. It is significant that the neurologist is the one who has insisted in the past on the unity of all convulsions, and, if he has excepted the "teething spasm" or tetany from his concept, perhaps this is rather from his own unacquaintance with these two conditions than a logical necessity. It is the pediatrician who for generations has urged the exclusiveness of the infantile fit.

I might venture yet further on the shifting sands of speculation and discuss the nature of the ultimate cause of convulsions. I have shown that a convulsion may be spontaneous, or that it may appear to be provoked by some obvious stimulus and that there is no correlation between the type or degree of stimulus and the convulsion. In certain persons, then, a certain stimulus will provoke a convulsion, but not in others; this stimulus varies in degree and kind in different subjects. Whether or not a person has a convulsion, therefore, depends on himself and not on any outside factors, save indirectly. In other words, one may postulate an inherent convulsive tendency which varies only in degree. In the highest degree it results in spontaneous convulsions or idiopathic epilepsy; at the other end of the scale only the provocation of a severe stimulus will produce the fit, such as in acute inflammation of the meninges, cerebral edema and tetany. Intermediate on

the epileptic side are those convulsions called by Stauder [15] "provoked epilepsy" in which a provoked convulsion is followed by spontaneous recurrence, while intermediate on the other side are the casual convulsions of infancy. Peterman [16] has already suggested that the high incidence of convulsions in childhood is due to the high incidence of acute infections in this period and it is not unreasonable to suppose that, in a person with a slightly lowered convulsive threshold, the concatenation of circumstances required to provoke a convulsion is most likely to occur in infancy and indeed will often happen only once in a lifetime. All convulsions are, therefore, fundamentally of one type, but for clinical work, and especially with regard to prognosis, some classification is necessary. I would classify them as (*a*) spontaneous or (*b*) provoked.

Spontaneous convulsions are those in which the convulsions occur in the absence of any apparent precipitating factor and depend entirely on the inherent convulsive tendency. They would, of course, include cases of idiopathic epilepsy and the convulsions associated *ab initio* with mental defect and usually with demonstrable developmental abnormalities of the brain. They would also include those resulting from permanent brain damage. Provoked convulsions are those in which the inherent convulsive tendency is insufficient to give rise to a convulsion in the absence of an adequate stimulus each time. Such convulsions are those associated with acute inflammation of the meninges, tetany and uremia and the initial convulsions of acute infections. Furthermore, in certain borderline cases a provoked convulsion will cause sufficient damage to the brain to tip the scale in favor of spontaneous convulsions thereafter.[15]

If one believes in the basic unity of all convulsions, there is no logical reason for not using the term "epilepsy" for all of them. One would then speak of spontaneous or provoked epilepsy. There is nothing in the previous argument against this, and it would, moreover, have the advantage of including explicitly petit mal, uncinate fits and epileptic equivalents. I am doubtful of the validity of including migraine, and in any case the question is not relevant to the present discussion. Other forms of epileptic response, however, could easily be attributed to slight differences in kind of the convulsive threshold.

The word "epilepsy," however, is firmly entrenched in clinical usage and has been since the days of Hippocrates; to extend its meaning so radically as to include all convulsions, major and minor, is to my mind quite unjustified and has, as I have shown, been the cause of

15. Stauder, K. H.: Krampfbereitschaft und Krämpfe des Kindesalters, München. med. Wchnschr. **86**:4, 1939.

16. Peterman, M. G.: Convulsions in Childhood: Study of Four Hundred and Nineteen Cases, J. A. M. A. **99**:546 (Aug. 13) 1932.

much misunderstanding. Instead the word "convulsion" can be retained in the classification but with the proviso that it must suggest a wider meaning and include other related seizures. For this reason, the term "epilepsy" is not used in so wide a connotation, but I should emphasize that the word is retained as describing a well known clinical picture and in no wise implies a fundamental basis differing from that of other convulsions.

The most that can be claimed for this classification is that it is simple and at least as accurate as many others. It may well be that rash speculation has been allowed to burst the bonds of prudence and that I have wandered far from the safety of observed facts. In extenuation I would point to the recent literature and suggest that "truth comes more readily from error than from confusion."

CONCLUSIONS

1. It is submitted that (*a*) all convulsions are primarily due to an inherent and often innate convulsive tendency and (*b*) this convulsive tendency varies in degree from that responsible for spontaneous recurrent convulsions (or idiopathic epilepsy) to that which is responsible for a convulsion only on the extreme provocation of gross cerebral irritation.

2. A simple classification of convulsions is, therefore, tentatively suggested, namely, that convulsions may be classed as either (*a*) spontaneous or (*b*) provoked.

3. The prognosis of infantile convulsions varies inversely with the degree of provocation.

Royal Hospital for Sick Children, Yorkhill (C.3).

Biochemical estimations were performed in the laboratory of Dr. H. E. C. Wilson, and Dr. D. Campbell Suttie gave access to hospital records.

Abstracts from Current Literature

Biochemistry; Bacteriology, and Pathology

EFFECTS OF AUTOXIDATION ON ANTIACRODYNIC POTENCY OF FATS AND LINOLEIC ESTERS. FRED A. KUMMEROW, TA-KUNG CHU and PATRICIA RANDOLPH, J. Nutrition **36**:523 (Nov.) 1948.

In this study, the ability of small quantities of oxidized fats and fatty acids to cure acrodynia was used as a means of testing their nutritive value. As pyridoxine, pantothenic acid and tocopherol have been reported to be functional in fat deficiency, these dietary factors were fed to some of the rats in the various groups. Furthermore, the effects of these factors and of oxidized fats on the characteristics of the mixed fatty acids deposited in the tissues were determined by means of spectrophotometric analysis. Kummerow and his associates observed that rancid methyl linoleate or the fat extracted from turkeys, which was subjected to cold storage for two years, alleviated the symptoms but were not as effective as the freshly distilled ester or fresh turkey fat. Tocopherol did not improve the effectiveness of rancid ethyl linoleate and ethanolamine aggravated the symptoms. Drastically oxidized fats or 10,12 ethyl linoleate were not effective curative agents. When pyridoxine and calcium pantothenate were fed in addition to rancid fat, the dermal symptoms were alleviated; this response was due to a combination of the fat-soluble and water-soluble factors. Spectrophotometric analysis of the carcass fats indicated that the various supplements of oxidized linoleic esters were converted to oleic and saturated fatty acids. Pyridoxine and calcium pantothenate seemed to be functional in this process.

FREDEEN, Kansas City, Mo.

EFFECT OF CARONAMIDE UPON PENICILLIN THERAPY OF EXPERIMENTAL PNEUMOCOCCUS AND TYPHOID INFECTIONS IN MICE. W. F. VERWEY and A. KATHRINE MILLER, Proc. Soc. Exper. Biol. & Med. **65**:222 (June) 1947.

Carinamide is the name given to 4'-carboxyphenylmethansulfonanilide, which delays the excretion of penicillin through the renal tubules, apparently by blocking the enzyme system in the tubules responsible for transport of penicillin through the cells. When given orally, this drug causes the blood levels of penicillin to go higher and remain so longer. In vivo studies with mice disclosed that the therapeutic effectiveness of penicillin to type I pneumococci was increased six to sixteen fold and to Eberthella typhosa fourfold when carinamide was given. This favorable effect is attributed to the higher and more prolonged plasma concentrations of penicillin when this drug is given.

HANSEN, Galveston, Texas.

INVASION BY SHIGELLA SONNEI OF TISSUES OF MICE FOLLOWING GAVAGE WITH VIABLE SHIGELLA. MERLIN L. COOPER and HELEN M. KELLER, Proc. Soc. Exper. Biol. & Med. **68**:87 (May) 1948.

A strain of Shigella paradysenteriae (sonnei), isolated several years previously from the stool of a child with bacillary dysentery, was given to mice by inserting infusion cultures into the esophagus. Within five to thirty minutes, cultures of the bacteria were obtained, most frequently from the central mesenteric gland and from the spleen, liver, kidneys, lungs and heart, but seldom from the tail blood.

After two hours, the bacteria were rarely isolated from these same tissues. The incidence of positive cultures obtained from the various tissues varied with both the size of the mice and the number of viable bacteria inserted into the esophagus.

HANSEN, Galveston, Texas.

Metabolism; Infant Feeding; Milk and Other Foods

DWARFISM IN HEALTHY CHILDREN: ITS POSSIBLE RELATION TO EMOTIONAL, NUTRITIONAL AND ENDOCRINE DISTURBANCES. N. B. TALBOT, EDNA H. SOBEL, BERTHA S. BURKE, ERICH LINDEMANN and SHIRLEY KAUFMAN, New England J. Med. **236**:783 (May 22) 1947.

In the past few years more than 100 abnormally short children have been encountered in the pediatric clinics of the Massachusetts General Hospital. In approximately 50 per cent of these patients, the stunted growth could be related to a definite disturbance in the pulmonary, cardiovascular, gastrointestinal, renal, hepatic, skeletal or endocrinologic systems. There remained, however, a group of 28 boys and 23 girls, 2½ to 15 years of age, in whom no such abnormality could be found. The present paper is the result of attempts to discover and eradicate the cause of stunted growth in such patients.

It was noted that several were grossly underweight for their height and that the great majority appeared to have scanty subcutaneous fat stores. Nutritional studies revealed that, although the intake of building materials, such as protein, was probably adequate for growth, the total caloric intake appeared to be undesirably low. In the majority of patients this predominantly caloric malnutrition appeared to be related to anorexia secondary to emotional disturbances. A few children failed to resume normal growth when the dietary inadequacies had been corrected. Furthermore, it was observed that the growth rate of both poorly nourished and well nourished dwarfs could be increased notably by the administration of a protein anabolic, or growth, hormone—methyl testosterone—without any evident change in diet. In a few well nourished dwarfs growth continued spontaneously at a satisfactory rate after one or two short courses of testosterone therapy. These observations suggested that the dwarfism in this group of children was due to a functional hypopituitarism occasioned by the limited caloric intake.

GENGENBACH, Denver.

NOTES ON BREAST FEEDING. ELIZABETH KIRK ROSE, in Senn, M. J. E.; Problems of Early Infancy, Transactions of the First Conference, March 3-4, 1947, New York.

A recent study showed the incidence of complete breast feeding at the Hospital of the University of Pennsylvania to be 45 per cent, as compared with 33 per cent in 25 of the other Philadelphia hospitals. The article seems mainly devoted to praising Sir Frederic Truby King's book "Feeding and Care of Baby."

McGUIGAN, Evanston, Ill.

CHEMICAL COMPOSITION OF EGYPTIAN BUFFALO'S MILK AND ITS RELATION TO MILK LAWS. AHMED GHONEIM, M. TAHA EL-KATIB and M. EL-MAGHRABI, J. Roy. Egyptian M. A. **30**:418 (Aug.) 1947.

The authors studied the composition of buffalo's milk for seven years and noted a wide variation in different animals and in the same animal on different days. It was observed that the fat content ranges from 4.1 to 12 per cent, with an average of 7.11 per cent. Nonfat solids vary from 7.9 to 10.9 per cent, with an

average of 9.63 per cent. The Egyptian milk laws require that the minimum figures for fat and nonfat solids should be 5 and 8.5 per cent, respectively. This requirement, in the authors' opinion, permits adulteration of a large proportion of the milk, and they recommend required figures of 5.75 and 9.25 per cent.

McGUIGAN, Evanston, Ill.

THE SUBACUTE SUBNUTRITIONAL SYNDROME IN INFANTS. MAMDOOH HANAFY, J. Roy. Egyptian M. A. **30:** 440 (Sept.) 1947.

The clinical effect of general undernourishment in infants is reviewed, and, although several clinical pictures may result from malnutrition, it is shown that they are all stages in the development of one syndrome. This the author calls the subacute subnutritional syndrome. A detailed description of the various states of the condition is given. Analysis of the symptoms indicates that the deficiencies are both multiple and varied. It is stated that after the condition has passed through a primary deficiency syndrome secondary changes lead to endocrine dysfunction, on which dietary treatment alone has no effect. Hanafy is of the opinion that infantile pellagra is a group of subnutritional manifestations and not a single entity.

McGUIGAN, Evanston, Ill.

SURFACE TENSION OF MILK. GIORGIO PICCARDI, Riv. di clinica pediat. **45:**385, 1947.

Experimental research has shown that the surface tension in the milk of animals (cow, she goat, ewe, she ass) varies spontaneously in the first minutes after milking, following which there is a rapid increase as in human milk.

The phenomena observed in animal milk are more pronounced than those in human milk. This has provided an opportunity for more precise understanding of the characteristics of surface tension. One may say that the change consists in a rapid fall of the surface tension, followed by an increase more or less rapid and continuous, i. e., a plunging of the tension. This plunging is likely to cause a rapid appearance on the surface of active substances initially free in the milk.

After these active substances become concentrated in the skim, one may separate the latter and dissolve it again in the skimmed milk. This causes a state of equilibrium (i. e., it has lost its activity) which engenders a second tension change in the same sample of milk.

The author discusses this phenomenon and compares it with others known in the field of surface chemistry and, particularly, with the antagonistic phenomena.

FROM THE AUTHOR'S SUMMARY.

CALCIUM AND PHOSPATE BALANCES AFTER ADMINISTRATION OF PURE CALCIUM SALTS AND PULVERIZED WHOLE BONE. HANS KÜNG, Ann. pædiat. **169:**111 (Aug.) 1947.

Resorption: If an increased quantity of calcium and phosphate is offered through the medium of a whole bone preparation (ossopan®), a calcined whole bone preparation and calcium gluconate, correspondingly more calcium and phosphate will be resorbed by the organism.

Retention: The action of the whole bone preparation persists beyond the period of administration, so that even in the after-period more calcium and phosphate are resorbed and retained than previously. However, the body discards again in the after-period the major portion of the resorbed calcium as soon as the calcined whole bone preparation or the calcium gluconate are added.

Tolerance: Without differentiation, all three preparations were readily taken by the children. No subsequent phenomena of any kind were observed.

If a whole bone preparation (ossopan®) is given, more calcium and phosphate are resorbed by the organism than when the calcined whole bone preparation or the calcium gluconate are administered, both during the period of administration and in the immediate after-period.

FROM THE AUTHOR'S SUMMARY.

Vitamins; Avitaminoses

INFANTILE BERI-BERI IN SINGAPORE DURING THE LATTER PART OF THE JAPANESE OCCUPATION. G. HARIDAS, Arch. Dis. Childhood **22**: 23 (March) 1947.

Infantile beriberi is avitaminosis B_1. It occurred in four forms: (*a*) aphonic; (*b*) peripheral neuritic; (*c*) acute cardiac and (*d*) pseudomeningeal. The clinical signs indicating a cardiac attack are dyspnea, cyanosis, tachycardia, dilatation of the right side of the heart, accentuation of the pulmonary second sound, enlarged liver and, in extreme cases, a congestive mottling of the skin.

It is not common in infants who are breast fed by mothers who are poor and who eat unmilled rice. It is common in the poor who eat highly milled rice.

Vitamin B_1 preparations administered parenterally have proved satisfactory in the treatment of this condition. The diet of the nursing mother determines the condition of her milk. The symptoms of vitamin B_1 deficiency in the mother are palpitations, creeping sensations, numbness and tingling in the lower extremities, weakness of legs, slight edema of ankles and tenderness of the calves, with absence of knee and ankle jerks.

KELLY, Milwaukee.

THE INFLUENCE OF HYPERVITAMINOSIS A ON BONE GROWTH. THOMAS E. VAN METRE JR., Bull. Johns Hopkins Hosp. **81**:305 (Nov.) 1947.

In order to determine the effect of hypervitaminosis A on the longitudinal growth of the long bones in the rat, the animals were given a fish oil concentrate containing vitamin A. This resulted in morphologic changes in the long bones interpreted as due to acceleration of normal processes: the acceleration of maturation, degeneration and death of epiphysial cartilage cells, formation of replacement bone and the acceleration of normal remodeling of the bone. The changes are in proportion to the dose of vitamin A given. Coincidental with these morphologic changes and again proportional to the amount of vitamin A given is a retardation of longitudinal bone growth. The experiments do not explain the reason this occurs.

LYTTLE, Los Angeles.

CONGENITAL RICKETS. A. REICHER, Pediatria **3**:30, 1946.

Results of an investigation on 1,004 newborn infants conducted over a period of twelve consecutive months are reported. All infants were examined during the first three days of life. Special attention was paid to the occurrence of congenital craniotabes and changes in the costochondral junctions. The results were as follows: Seven hundred and seventy-four infants, or 76.8 per cent, presented some changes of the costochondral junctions, which varied from a linear thickening (526 infants) to a rounded thickening suggestive of rachitic beading (28 infants). Frank craniotabes of the parchment or mushy varieties occurred in 96 infants, while minor forms were observed in 23 infants, thus bringing the total incidence of congenital craniotabes to 11.5 per cent.

Congenital craniotabes was limited almost entirely to the parietal bones, the vertex being the region primarily involved. Both parietal bones were affected in 51

infants, the left alone in 26 infants and the right alone in 19. The incidence of linear changes in the costochondral junctions was not appreciably higher among infants with craniotabes. The incidence of the changes suggestive of beading of the ribs, however, was definitely higher among infants with craniotabes. Congenital craniotabes also showed a variation in seasonal incidence analogous to that of rickets. Thus, the incidence of congenital craniotabes was highest in winter and spring and lowest during the period from July to September. All infants with congenital craniotabes were apparently full term and of normal weight at birth. Congenital craniotabes occurred more frequently among offspring of primiparas.

Thirty infants with congenital craniotabes were followed for two months. In 19 infants the craniotabes subsided spontaneously at the age of 4 to 6 weeks. In 11 infants who also showed suggestive beading of the ribs, congenital craniotabes could still be observed at the age of 8 weeks. This group of infants also showed an associated early development of postnatal, or so-called rachitic, craniotabes.

Blood calcium and phosphorus determinations were made on 39 newborn infants with congenital craniotabes, with 164 apparently normal newborn infants as controls. The normal standards thus established for the blood calcium and phosphorus levels in the newborn were 9 to 10 mg. per hundred cubic centimeters for calcium and 5 to 6 mg. per hundred cubic centimeters for phosphorus. According to these standards, 18 of the 39 infants with congenital craniotabes showed slight alterations in the blood calcium level, whereas all 39 infants showed definite alterations in the blood phosphorus level. In fact, more than half showed blood phosphorus values below 3 mg. per hundred cubic centimeters.

The variation in seasonal incidence of congenital craniotabes, as well as its frequent association with beading of ribs and alterations in blood calcium and phosphorus, forms the basis for the following conclusions: 1. Linear thickening of costochondral junctions in the newborn is physiologic. 2. Congenital rickets may exist at birth. 3. Congenital craniotabes is a valuable sign of congenital rickets.

BEDER, Los Angeles.

Hygiene; Growth and Nutrition; Public Health

HEIGHT AND WEIGHT IN RELATION TO ONSET OF PUBERTY IN BOYS. RICHARD W. B. ELLIS, Arch. Dis. Childhood **21**: 181 (Dec.) 1946.

Two hundred and eight boys, 11 to 16 years of age, from two residential schools, were graded on a basis of clinical assessment into three maturity groups, prepubescent, pubescent and adolescent. Comparison was made of the mean heights and weights of boys from the same school who fell into the same yearly age groups but into different maturity groups.

It was found that not only were boys of the higher maturity group heavier and taller than their contemporaries in the lower maturity group, but that differences between the curves for the growth could be demonstrated as far back as the sixth year (in the case of boys from one of the schools, where records were available from that time).

The growth curves suggested an increased annual gain in weight and, to a lesser extent, in height, which could be related to the onset and duration of puberty. This was confirmed by the reexamination of the boys of one age group after a period of one hundred days, when it was observed that increase in height and weight of pubescent boys was significantly greater than that of prepubescent boys in the same school.

KELLY, Milwaukee.

SOME OBSERVATIONS ON THE GROWTH OF CHILDREN. G. M. ALLEN-WILLIAMS. Arch. Dis. Childhood **21**:190 (Dec.) 1946.

Although the data relating to infants under 1 year of age in this investigation are few in number, they appear to suggest that the period of greatest growth occurs in the latter half of the first year of life. Among children up to 5 years of age, growth in boys is, on the whole, greater—but not significantly greater—than in girls.

The highest degree of relationship among the variables observed is found between the sitting height and the weight. In children up to 4 years of age, the width of the pelvis is more closely correlated with the weight than with the sitting height, but this relation alters with age, so that in those at 4 to 5 years of age the width of the pelvis is more closely related to the sitting height. KELLY, Milwaukee.

SOCIO-EMOTIONAL FACTORS ACCOUNTING FOR GROWTH FAILURE IN CHILDREN LIVING IN AN INSTITUTION. R. FRIEL and M. F. MAYER, J. Pediat. **33**:444 (Oct.) 1948.

This study, which was carried out in an institution for Jewish children classed as dependent or neglected, reveals that a close correlation existed between disturbances in growth and development, as revealed by comparison with the Wetzel Grid, and socioemotional problems. Malnutrition and obesity were the most commonly encountered disturbances, and they could not be corrected by purely physical measures. The authors are of the opinion that socioemotional factors played a significant role in all growth difficulties. This they report to be true whether the growth defect or the emotional problem presented was the primary problem. Their data support the view that progress in the adjustment of emotional problems in the population studied was reflected in improved physical growth and development as measured on the Wetzel Grid. GRULEE JR., Galveston, Texas.

OUTLINES FOR WELL BABY CLINICS: II. RECORDING DEVELOPMENT OF SECOND TWELVE MONTHS. EDITH S. HEWITT and C. ANDERSON ALDRICH, Pediatrics **2**:69 (July) 1948.

At the ages of 14, 16, 18, 21 and 24 months, significant developmental steps may be noted in the (1) motor ability, (2) eating, (3) sleeping, (4) elimination and (5) social adjustment of a child. This paper sets forth the steps discernible at the various months in such a way that the physician can transfer the details to cards and use them as desk guides when examining children. To relate the progress at each age mentioned is impossible in an abstract. However, at the end of the second year the progress made in the various activities may be noted as follows: 1. The child can walk, run, climb and jump, can go backward and sideways as well as forward and can use his small muscles with considerable skill. 2. The child accepts a large variety of foods and feeds himself well. 3. He usually sleeps through the night without awakening and takes one nap in the daytime. Bedtime rituals are to be expected. 4. He usually takes the responsibility for bowel and bladder control in the daytime, but accidents may occur. 5. He has learned much about conformity but still is not cooperative. Though his attention is becoming more organized, it is still transitory. FROM THE AUTHORS' ABSTRACT.

Prematurity and Congenital Deformities

CARBONIC ANHYDRASE IN THE CENTRAL NERVOUS SYSTEM OF THE DEVELOPING FETUS. W. ASHBY and E. BUTLER, J. Biol. Chem. **175**:425, 1948.

Well defined patterns of quantitative distribution of carbonic anhydrase have been reported in the central nervous system of man and of animals. Two reports

have been made on deviations from the normal pattern of distribution in man incident to mental disease. As part of an effort to elucidate the significance of this enzyme in the central nervous system, a study of its fetal distribution was undertaken. In the normal fetal calf, the following observations were made: (1) a progressive caudal to rostral increase in the enzyme, approaching the adult pattern; (2) absence of the enzyme from the cerebrum until late in fetal development, in contrast to other enzymes studied in the fetal central nervous system; (3) from the seventh month to birth, except for its absence in the pallium, a repetition of the pattern of relative content of the enzyme, with an approach in magnitude to the level found in the adult. An early appearance of the enzyme was found in the blood of the fetal calf, in contrast to the finding of Meldrum and Roughton for fetal goats. In the premature and the full term human infant the data indicate (1) a caudal to rostral increase in the enzyme with increase in age; (2) a less complete approach to the adult pattern of distribution in the full term infant than in the six month calf fetus; (3) no carbonic anhydrase in the cerebrum at birth. The possibility that the absence of carbonic anhydrase from the cerebrum of the full term human infant studied may have been abnormal is considered.

PAGE, Cleveland [Arch. Neurol. & Psychiat.],

THE BRAIN IN A CASE OF HUMAN CYCLOPIA. OTTO MARBURG and FRANCIS J. WARNER, J. Nerv. & Ment. Dis. **103**:319 (April) 1946.

Marburg and Warner studied the microscopic features of the brain in a case of human cyclopia and compared their observations with those in the case of Marburg and Mettler. The brain stem as high as the diencephalon was normal except for the loss of cortical pathways. Although the optic nerves were present in the eye, there was no optic chiasm. A thick connective tissue membrane covered the floor of the third ventricle as far as the infundibular funnel. In the telencephalon, except in the occipital lobes, there was only one ventricular lumen. The olfactory bulbs and tracts and the striae olfactoriae were destroyed.

Destruction of the secondary olfactory systems is followed by absence of the peripheral olfactory apparatus. Subsequently, a change in the skeleton occurs, with development of a common orbit and one eye, or two eyes fused in the midline, as in this case. Preservation of the central olfactory system, the habenula, the mamillary bodies and the fornix is evidence of the independent development of these structures. The pathologic process leading to the production of such monsters involves the germ plate in the first four weeks of fetal development.

CHODOFF, Washington, D. C. [ARCH. NEUROL. & PSCHIAT.]

CONGENITAL ALVEOLAR DYSPLASIA: A DEVELOPMENTAL ANOMALY INVOLVING PULMONARY ALVEOLI. H. EDWARD MACMAHON, Pediatrics **2**:43 (July) 1948.

This paper described a disturbance in the growth and development of pulmonary alveoli, characterized by a disproportion between the size of the alveolar spaces and the thickness of their walls. The walls were too thick and the spaces too small. Resilience was diminished and pulmonary circulation was impaired. It was the opinion of the author that this anomaly, which may be observed in premature and in full term infants, can lead to progressive cyanosis and death within the first forty-eight hours of life. The causation of this lesion is obscure, but its pathogenesis appears to lie in a disturbance in growth associated with a retardation in alveolar development. FROM THE AUTHOR'S SUMMARY.

INFLUENCE OF POSTNATAL AGE ON KIDNEY FUNCTION OF PREMATURE INFANTS. HENRY L. BARNETT, W. KENDRICK HARE, HELEN MCNAMARA and RUTH S. HARE, Proc. Soc. Exper. Biol. & Med. **69**:55 (Oct.) 1948.

Measurements of renal function were made in two groups of 17 premature female infants, weighing 2,130 to 2,520 Gm., in one group for three to thirteen days and in the other for forty-nine to one hundred and seven days. The latter group did not differ greatly in weight from the first; hence they were small at birth (820 to 1,360 Gm.). For comparison with adult values the means for each group were corrected for surface area. Respectively for the former and latter groups, the inulin clearances were 41 and 58 per cent, para-aminohippurate clearances 25 and 34 per cent and the para-aminohippurate tubular maxima 17 and 27 per cent. The ratio of the inulin clearance and para-aminohippurate clearance was almost identical in both groups. The authors suggest that development of renal function in infants weighing up to 2,500 Gm. may be influenced by a gestational factor not operating in larger infants.

HANSEN, Galveston, Texas.

INIENCEPHALUS. D. F. OSBORNE, Canad. M. A. J. **59**:474 (Nov.) 1948.

Two cases of iniencephalus are presented which showed the classical triad of fetal retroflexion, deficiency of the occiput and rachischisis of variable extent. The incidence was 1 in 1,730 deliveries.

MCGUIGAN, Evanston, Ill.

OXYCEPHALY. PHILIP EVANS, Proc. Roy. Soc. Med. **40**:166 (Feb.) 1947.

The patient, a boy 7 months of age, was noticed at birth to have an abnormally shaped head. On examination the child was healthy. The circumference of the head was 16¼ inches (41.3 cm.). The appearance was typical of oxycephalia without exophthalmos. The anterior fontanel admitted the finger tip; the metopic suture was not felt, but the other suture lines were palpable. The child was bright, cheerful and without visual disturbance.

WILLIAMSON, New Orleans.

THE PREMATURE INFANT. J. LEGROS, Acta pædiat. belg. **1**:82, 1946-1947.

The author attributes the increase in infant mortality in Belgium to the higher number of prematurely born babies, and this fact in turn to the necessity for mothers to do heavy work during pregnancy. Every day of intrauterine life is of great importance, especially since so much of the baby's growth occurs during the last fetal months. The most important factors in the survival of premature infants as mentioned are: (1) an experienced and conscientious nurse; (2) minimal manipulation of the baby; (3) avoidance of chilling (the incubator is not considered convenient; instead the room temperature is kept between 22 and 26 C. [71.6 and 78.8 F.]); (4) regulation of humidity; (5) avoidance of aspiration of food and (6) observation of respiration.

On this last factor Legros has made a study of different medicaments. By utilizing a pneumograph, he graphically charted the response of the respiration to lobeline metrazol,® nikethamide N. N. R., carbogen® (a mixture of carbon dioxide and oxygen). Metrazol® and nikethamide gave unsatisfactory results. Caffeine increased the amplitude of the respiration but had no effect on regularity. Lobeline had good effect on rhythm as well as strength, and, if combined with carbogen® (five minutes of every hour), its effect could be prolonged. As food Legros suggested mother's milk enriched with calcium paracaseinate from the twenty-first day of life. Since the milk loses some of its qualities by boiling, fractional sterilization

is suggested (heating to 65 C. [149 F.] for half an hour on five consecutive days). The author demonstrates, by giving the death rates of the last few years, that the utilization of breast milk reduces the mortality rate.

GLASER, Chicago.

DEMOGRAPHIC STUDY OF MORTALITY DUE TO PREMATURITY AND CONGENITAL WEAKNESS IN BUENOS AIRES, ARGENTINA, 1937 TO 1941. D. AGUILAR GIRALDÉS, Arch. argent. de pediat. **27**:106 (March) 1947.

Of a total of 4,426 deaths, 48.91 per cent were due to prematurity and congenital weakness.

ROJAS, Boston.

Newborn

THE CLINICAL APPLICATION OF THE RH FACTOR. E. T. MCENERY, G. R. BABA and K. TOGASKI, Illinois M. J. **94**:99 (Aug.) 1948.

From October 1944 to December 1946, 2,372 women who were delivered at the Lewis Memorial Maternity Hospital, Chicago, had determinations of the Rh factor. Of these, 223 had Rh-negative reactions. Twelve of the babies delivered of the Rh-negative mothers had complications. All the 12 babies and their fathers were Rh positive.

Clinically, it was difficult to tell when complications were developing in one of these babies. Routinely, complete blood counts were made on the second day with determinations of the Rh reaction and blood group of the child. If the red blood cell count was dropping and the number of normoblasts increasing, transfusions of Rh-negative compatible blood were given. Regardless of the laboratory report, one should be guided clinically by the condition of the baby. One is always safe in giving a transfusion of Rh-negative blood.

BARBOUR, Peoria, Ill.

TRANSFUSIONS IN NEWBORN INFANTS THROUGH ABDOMINAL WALL SEGMENT OF UMBILICAL VEIN. L. R. PINCUS, J. Pediat. **33**:418 (Oct.) 1948.

By making a 2 cm. transverse incision 1 cm. cephalad to the umbilicus, and by then cutting the midlying aponeurosis in a sagittal plane to each side of the umbilical vein, a cannula can be introduced into the latter, and transfusion accomplished. This technic is suggested particularly for exchange transfusion when the umbilical vein is no longer patent in the umbilical cord. How long this segment of umbilical vein lying in the abdominal wall, but extraperitoneally, can be used after birth has not been determined.

GRULEE JR., Galveston, Texas.

THE SIGNIFICANCE OF POSITIVE BLOOD CULTURES IN NEWBORN INFANTS. W. W. WADDELL JR., R. E. BAKLY and W. GROSSMANN, J. Pediat. **33**:426 (Oct.) 1948.

The authors report their observations on 320 blood cultures from 240 infants. The high incidence of coagulase-negative Staphylococcus albus hemolyticus among infants showing inordinate loss of weight, anorexia and restlessness, the frequency with which the same organisms could be isolated on repeat culture and the response of these infants to penicillin therapy, with the disappearance of the organism from blood cultures, were striking. Because the authors realize that the organism in question is generally not considered pathogenic, and because it is the organism most commonly found as a skin contaminant, they are of the opinion that their

results must be interpreted with qualification. However, they do not express a belief that the observations are explainable on the basis of contamination of skin and subcutaneous tissue. The results of their control studies support this premise.

GRULEE JR., Galveston, Texas.

CARE OF THE TOXIC NEWBORN. J. D. RUSS, New Orleans M. & S. J. **101**:292 (Dec.) 1948.

It is pointed out that the outlook for babies born of toxic mothers may be improved by careful delivery room technic, including attention to anesthetization, duration of labor, administration of oxygen to the mother and proper resuscitation of the baby.

McGUIGAN, Evanston, Ill.

REPRODUCTIVE HISTORIES OF THE MOTHERS OF THREE HUNDRED AND TWENTY-TWO INFANTS WITH ERYTHROBLASTOSIS. EDITH L. POTTER, Pediatrics **2**:359 (Oct.) 1948.

The 175 women observed from 1934 through 1947, who became immunized to the Rh factor, had a total of 699 pregnancies: 341 preceding the birth of the first infant with erythroblastosis, resulting in 7 stillbirths, 13 neonatal deaths, 65 abortions and 256 surviving children. Of the abortions, 44 followed the birth of the last normal child and preceded that of the first child with erythroblastosis. The average number of surviving children born to each patient before the birth of an infant with erythroblastosis was 1.4.

Diagnosis of erythroblastosis was made for the first time in 7 women in first and 168 women in second or subsequent pregnancies. Four of the women without earlier pregnancies had had transfusions. Of the 178 affected infants, 56 died before birth, 60 died after birth and 62 survived.

Ninety-six women had 179 pregnancies following the birth of an infant with erythroblastosis, resulting in the birth of 3 Rh-negative (normal) infants, 144 Rh-positive infants with erythroblastosis and 32 abortions, 13 known to be induced. Of the Rh-positive infants, 69 were stillborn, 63 died and 12 survived, 3 of which have brain damage. The 322 infants with erythroblastosis included 158 boys, 132 girls and 32 of unknown sex. Survival was 28 per cent for boys and 23 per cent for girls.

Among 131 infants with erythroblastosis delivered of this series of patients, mortality rates were: 38 per cent for 58 infants whose birth had not been immediately preceded by a transfusion, abortion or erythroblastosis; 74 per cent for 26 infants whose birth was immediately preceded by an abortion or transfusion, and 90 per cent for 46 infants whose birth was preceded by that of an infant with erythroblastosis.

Among 18,468 deliveries in the last five years, the frequency with which erythroblastosis occurred for the first time varied from 1:2,814 in first pregnancies to 1:172 in second pregnancies and 1:55 for sixth pregnancies. In the last two years, no liveborn infant in this series died of erythroblastosis who did not have an older affected sibling.

In evaluating any treatment, previous maternal reproductive histories of the infants must be considered. In this series previous maternal history was of more value in prognosticating the fate of an infant born to an immunized Rh-negative woman than were changes in maternal antibody titer or differences in the variety of antibodies present.

FROM THE AUTHOR'S SUMMARY.

CUP FEEDING OF NEWBORN INFANTS. ROBERT C. FREDEEN, Pediatrics **2**:544 (Nov.) 1948.

A personal experience in feeding several hundred newborn babies from a cup or glass during the past ten years is reported. The gains in weight made by premature infants and infants with oral defects, such as harelip and cleft palate, indicate that this is a satisfactory method of feeding for these special groups. Although no statistics can be cited, it is the author's opinion that full term infants suffer no psychologic harm in subsequent years as a result of having been deprived of the more strenuous sucking experience that probably accompanies bottle and breast feeding. It is his feeling that infants who are started on feeding from the cup early in life avoid the emotional difficulties that sometimes accompany the introduction of solid foods and the weaning process.

FROM THE AUTHOR'S SUMMARY.

LOCAL PENICILLIN THERAPY IN OPHTHALMIA NEONATORIUM. ARNOLD SORSBY, Brit. M. J. **1**:903 (June 30) 1945.

In practically all cases reported on here cultures were made, the organism varying from gonococcus to virus. The rapid method of treatment used consisted essentially in wiping pus from the baby's eyes and instilling 1 drop of penicillin, 2,500 units per cubic centimeter, in each eye at five minute intervals. This was continued until no further pus was formed. Usually, six to thirty applications were necessary. Following this, penicillin was put in the eye at one-half hour intervals until the eye appeared normal. Usually, this occurred in six to twelve hours. After this, penicillin was instilled hourly for twelve hours and then at two hour intervals for twenty-four hours.

According to the summary, this local therapy proved effective in 21 of 22 patients with ophthalmia neonatorum reported on previously. In a further series of 38 patients reported on here, 2 failed to respond. Twenty-five of the 38 patients had been treated by intensive application of penicillin (with drops instilled every five minutes). The results were better than those obtained by the instillation of penicillin at half-hour intervals (as in 22 children previously reported on) or at hourly intervals (as in 13 in the present series).

The 25 children treated intensively included 2 who showed no response and 5 who relapsed after initial clinical cure; 4 of these 5 who showed relapse responded well to a second course of treatment with penicillin. Of the 18 infants who responded initially to treatment, 13 showed clinical cure within twelve hours and a further 4 within twelve to twenty-four hours.

Severity of the clinical condition does not appear to affect the duration of treatment. Penicillin is effective against all the common causal organisms of ophthalmia neonatorum, including the presumed virus of inclusion blennorrhea. Local penicillin therapy is likely to replace general sulfonamide treatment as the method of choice in ophthalmia neonatorum.

BIRDSONG, University, Va.

TWO RARE CASES OF HEMOLYTIC DISEASE OF THE NEWBORN. K. RASKA, M. TUTTER and K. KUBÁT, Pediat. listy **2**:164, 1947.

The first case was of a woman (blood type A_1, MN-p-r) in whom Rh isoimmunization was observed simultaneously with anti-P isoimmunization (father's blood was type A_2, MN-P-R_1), which caused a hemolytic illness of mild degree in the fourth child (blood type O, MN-P-r). Cure quickly followed discontinuation of breast feeding and transfusions of Rh-negative blood.

In the second case (blood type B, MN-r′) anti-R_1 isoimmunization was observed in the woman, as was isoimmunization against a further unknown antigen of human red blood corpuscles, in addition to those of the known systems (father's blood was type B, M-R^1). The authors' patient was the sixth child (blood type O, MN-r′). Three boys had died with symptoms of fetal erythroblastosis (with factor R^1); three girls (with factor r′) had survived, and only the last child had icterus gravis. She was cured by transfusions of suitable blood. A detailed serologic analysis in both cases is being undertaken.

FROM THE AUTHORS' SUMMARY.

NEONATAL MORTALITY IN SLOVAKIA. A. NOVÀK, Pediat. listy **2**:181, 1947.

During 1945 the average figure for neonatal mortality was 169.5 per thousand (with a variation according to districts of between 105.7 and 254.7 per thousand). In the struggle against infant mortality, Slovakia was divided into districts, with a pediatrician as head of each.

FROM THE AUTHOR'S SUMMARY.

HYPOPROTHROMBINEMIA AFTER THE NEWBORN PERIOD. S. URWITZ, Nord. med. (Hygiea) **30**:777 (April 5) 1946.

Six cases are reported of hypoprothrombinemia in infants from 1 week to 7½ months of age. The cause of the disorder was biliary stasis, hepatic deficiency in a premature infant, vomiting and diarrhea and chronic intestinal deficiency; in the sixth case the cause was unknown. In addition, the author reports on a case of esophageal atresia and on a case of atresia of the biliary ducts without any sign of hypoprothrombinemia.

WALLGREN, Stockholm, Sweden.

ENTEROCOCCI IN INFECTIOUS DIARRHEA OF THE NEWBORN. OLLE HENSCHEN NYMAN, Nord. med. **30**:1133 (May 24) 1946.

Four of 6 infants with neonatal diarrhea were examined bacteriologically, and hemolytic enterococci were demonstrated in all 4. With complement fixation tests the organisms were proved to belong to the same serologic type. Serum from 1 of the surviving infants agglutinated the enterococci in a titer of 1:740 and one week later in a titer of 1:1,280, which is considered an indication that enterococci may play an etiologic role in infectious diarrhea of the newborn.

WALLGREN, Stockholm, Sweden.

BACTERIOLOGIC AND EPIDEMIOLOGIC STUDIES ON PEMPHIGUS NEONATORUM AND ITS TREATMENT. STEN WINBLAD, HJALMAR TRIER and CARL TROPÉ, Svenska läk.-tidning. **43**:2476 (Oct. 4) 1946.

A report is presented on four small epidemics of pemphigus neonatorum at maternity hospitals. In all cases Staphylococcus aureus was demonstrated in the blebs. In three of the epidemics pathogenic staphylococci were seen in material from the nose of the nurses attending the ward; this is considered the source of infection. A nurse with staphylococci in her upper respiratory tract should be kept away from the infants' ward. Bathing of the newborn has no noxious effect, as there was no difference in the incidence of pemphigus among infants who had been given a bath and the alternate infants who had not been bathed.

WALLGREN, Stockholm, Sweden.

Acute Infectious Diseases

DIAGNOSIS OF ENTEROBIASIS. LUIS MAZZOTTI AND MARIA TERESA OSORIO, J. Lab. & Clin. Med. **30**:1046 (Dec.) 1945.

Examinations for the diagnosis of oxyuriasis were carried out on 430 persons, with the use of both of the NIH swab (Hall) and "Scotch" cellulose tape loop (Graham) technics. The proportion of positive results obtained was 32 per cent with the Graham method and 16 per cent with the technic of Hall.

WILKINSON, Galveston, Texas.

BOUILLAUD'S DISEASE (ACUTE RHEUMATIC FEVER) IN SMALL CHILDREN. R. POINSO AND J. M. LAUGIER, Pediatrie **35**:34 (Jan.-Feb.) 1946.

The authors are particularly interested in describing the infrequently occurring cases of acute rheumatic fever in very young children. The special features of the disease at this age are (1) a usual absence of involvement of the joints, (2) regular presence of cardiac involvement with all parts of the heart affected, especially the myocardium, (3) early death in almost all cases and (4) resistance to treatment, particularly with sodium salicylate.

The symptoms of the pathologic changes in the joints are as follows: (*a*) absence of all evidences of disease in the joints, which situation leaves observations of the heart or lung alone for diagnosis and often makes diagnosis impossible before post-mortem examination; *(b)* delayed articular symptoms, often appearing after as much as one month; *(c)* the possible presence of severe, brief pains in the muscular regions of the arms and legs, rather than in the joint areas, or *(d)* regular migrating joint pains, which respond to salicylates, like those in older children. The last possibility is rare.

Cardiac findings associated with rheumatism in young children are dominant. The beginning of the disease may manifest itself by heart failure. Valvular lesions are almost always mitral and of the type producing insufficiency. A very loud systolic murmur and/or rapid cardiac enlargement may be found. There are relatively few signs of peripheral cardiac failure, in spite of the considerable cardiac lesion. The occurrence of rales in the bases of the lungs is believed to be due to direct involvement of the lungs by the virus of rheumatic fever. Probably the most characteristic clinical finding of rheumatism in the very young is cardiac insufficiency, acute or subacute, which leads to death. The authors try to explain the major cardiac involvement by a possible primary focus of the virus of rheumatic fever in the heart. Cardiac involvement occurs in 100 per cent of small children with rheumatic infection, in 72 per cent of older children and in 10 per cent of persons 20 years of age. The authors believe that the absence of a cardiac defense mechanism in the very young is the explanation of this situation.

The prognosis is very poor. Rapid death occurs through cardiac failure. The disease does not respond to classic therapy. Salicylates have no effect, may produce acidosis or, when injected intravenously, may cause sudden death by pulmonary edema. Complete bed rest, a diet high in glucose (to avoid glycogen depletion of the liver under the effect of salicylate therapy and to increase the glycogen of the heart muscle), the reduction of liquids, frequent and small meals, and an ice bag placed over the heart have been employed. Sodium salicylate or antipyrine is used as antirheumatic therapy, together with autohemotherapy or vaccinotherapy (anti-rheumatic fever vaccine of Bertrand or "cardiostreptine"). As cardiotonic therapy

the following means have been used: ouabain intravenously, slowly injected with repeated aspiration of blood in a syringe in order to establish the mixture, soluble camphor, bleedings, scarifications and catharsis.

GLASER, Chicago.

SIZE OF HEART DURING RHEUMATIC FEVER IN CHILDREN. J. R. DIAZ NIELSEN, Arch. argent. de pediat. **25**:424 (June) 1946.

The roentgenographic silhouette of the heart becomes enlarged, as a rule, during rheumatic heart disease. In exceptional cases such enlargement does not occur. The cause of the enlargement is total myocardial dilatation. The valvular lesions are not the cause, since the valves are not yet organized. The dilatation takes place early in the development of the child's heart; and the severer the carditis, the more noticeable the dilatation. The myocardial dilatation may be the only cause of murmur detectable on auscultation.

The dilatation may be detected by the measurement of the transverse diameter of the heart, especially if this is made in a series of teleroentgenograms. The charts, elaborated on by the author, were useful in all cases; they gave the transverse diameter according to sex, age, height and weight.

The cardiothoracic coefficient is the best guide in obtaining information on the size of the heart in a single teleroentgenogram.

The increase in size of the cardiac silhouette is the sign of an active process. The cardiac enlargement may stop, or even become normal; on the contrary, in cases of malignant type it may be progressive and irreducible.

In case of inactive residual cardiopathy, the size and shape of the heart are determined by the compensatory hypertrophy and dilatation of the valvular lesions; in such instances, the size cannot be evaluated by measuring the transverse diameter in a single anteroposterior roentgenogram because of deformity in the individual chambers.

FROM THE AUTHOR'S ABSTRACT.

TREATMENT OF A CASE OF SEVERE TETANUS. G. FANCONI, Helvet. pædiat. acta **2**:177 (April) 1947.

The author reports the therapy used in a case of severe tetanus, with frequent spontaneous and reflex spasms and with prolonged high fever. The child recovered. As sedative drugs, "cloettal" and "pantopon hydrochloride" (a proprietary opium preparation containing the total opium alkaloids in the form of soluble hydrochlorides) were given; as antibiotics, penicillin and sulfapyrimidine. Compression deformities of several dorsal vertebrae developed as a consequence of the severe tetanic spasms.

FROM THE AUTHOR'S ABSTRACT.

Chronic Infectious Diseases

BCG VACCINATION IN SCANDINAVIA: TWENTY YEARS OF UNINTERRUPTED VACCINATION AGAINST TUBERCULOSIS. KONRAD BIRKHAUG, Am. Rev. Tuberc. **55**:234 (March) 1947.

BCG vaccination of a rapidly increasing population of negative tuberculin reactors, intimately exposed to tuberculous infection, has become an established public health measure in Norway, Sweden and Denmark since 1926. The experience of various workers in this field in Scandinavia during the past twenty years and the results of attempts to control tuberculosis by means of vaccination are reviewed in this paper.

A remarkable shift has been observed in the age period that primary tuberculous infection takes place. At the turn of the century, about 50 per cent of persons between 10 and 15 years of age were tuberculin reactors and almost 90

per cent of those between 25 and 30 years. In 1944, the percentages were 20 and 50 per cent respectively, and the peak of incidence was observed in the group 20 to 30 years of age. It was also noted that the acute and rapidly fatal exudative type of tuberculosis has become unexpectedly common among adolescents and young adults who did not react to tuberculin.

In the control of this advanced shift in the time of primary tuberculous infection, BCG vaccination has proved its worth, since such vaccination is completely harmless and produces a mild tuberculin reactivity and a relatively high protection against exogenous infection with virulent tubercle bacilli.

The favorable reports of BCG vaccination are resulting in a wider use of this measure in all the Scandinavian countries. The National Tuberculosis Association of Norway has enacted a law making obligatory the vaccination of every negative tuberculin reactor in the eighth grade of the public schools. BCG vaccination has been carried on in an increasing scale in Sweden, and in Denmark all school children between 10 and 14 years of age were vaccinated during 1946 and 1947, provided they were negative reactors to tuberculin.

On the basis of this extensive and long-continued use of BCG vaccination, observers in these countries conclude that BCG vaccination renders the reactions of 90 per cent of nontuberculin reactors positive to tuberculin within two months after vaccination. In the absence of known tuberculous infection, the duration of allergy following vaccination lasts more than five years, although in some instances it may terminate in one year. During the period of BCG vaccination, allergy and exposure to known tuberculous infection, BCG affords an almost complete protection against the morbid postprimary tuberculous lesions and relatively high protection against secondary tuberculosis including clinical pulmonary disease.

BCG vaccination does not imply any risk whatsoever of a subsequent infection caused by the vaccine and yet it accomplishes almost the same protective function against tuberculous disease as does a natural infection with virulent tubercle bacilli. As an adjunct to the time-honored antituberculous measures, BCG vaccination commends itself as an effective weapon against the disease among the especially susceptible tuberculin contacts of a tuberculous population.

SMITH, Ogden, Utah.

TUBERCULOUS ABSCESS FORMATION FOLLOWING PENICILLIN THERAPY. J. C. R. HINDENACH, Proc. Roy. Soc. Med. **40**:161 (Feb.) 1947.

A boy 2 years 9 months of age was admitted to the hospital with an indurated swelling in the left side of the neck of one week's duration. The swelling was incised, the pus found being sterile on culture with a few gram-positive cocci seen on direct smear. Penicillin in isotomic sodium chloride solution was given by injection into the thigh and buttocks. The wound healed and the child was discharged from the hospital on the eleventh day. Fifteen days later he was readmitted with abscesses in left thigh, groin and right buttock. Pus from all three abscesses contained tubercle bacilli and was sterile on culture. Results of the investigations made and discussion on the mode of infection by the tubercle bacilli follow in the report.

WILLIAMSON, New Orleans.

CONGENITAL SYPHILIS. MARY WILMERS, Proc. Roy. Soc. Med. **40**:161 (Feb.) 1947.

This is the case of an infant 2 months of age. The baby had had a thick, purulent nasal discharge since birth. Peeling of the hands and feet was noticed for three weeks. Physical examination revealed a typical syphilitic child with

enlarged liver and spleen, anal fissures, maculopapular rash and early rhagades. The Wassermann and Kahn reactions were positive in both the mother and the baby. The treatment given first was mercury inunctions, with no improvement. Two weeks later a total dose of penicillin, 120,000 units per kilogram of body weight, was given in 60 doses at four hourly intervals, combined with daily mercury inunctions. In three days the general condition was much improved and a gain in weight noticed.

WILLIAMSON, New Orleans.

USE OF DUBOS MEDIUM FOR CULTURE OF M. TUBERCULOSIS FROM SPUTUM. HORACE GOLDIE, Proc. Soc. Exper. Biol. & Med. **65**:210 (June) 1947.

Four hundred specimens of sputum were treated with a 2.5 per cent solution of ammonium carbonate incubated at 37 C. (98.6 F.) for four hours, placed in shakers and then centrifuged. A portion of this was added to Dubos synthetic medium (Dubos, R. J.: *Proc. Soc. Exper. Biol. & Med.* **58**:361, 1945; *J. Exper. Med.* **83**:409, 1946) with 0.2 to 0.3 cc. of albumin solution. To the incubated tubes, penicillin solution (0.5 to 2.0 units per cubic centimeter) was added and they were then incubated at 37 C. Smears from the cultures were prepared and examined one to two weeks later. In no case was the sputum positive by microscopic examination and negative on culture. Thirty-four (8.5 per cent) were positive by the culture method and negative by microscopic examination. The author states that this method is easily learned, inexpensive and relatively rapid (eight to fifteen days) for sputums containing relatively small numbers of Mycobacterium tuberculosis.

HANSEN, Galveston, Texas.

SERUM CALCIUM AND BLOOD INORGANIC PHOSPHORUS LEVELS AFTER MASSIVE THERAPY WITH VITAMIN D_2 IN CHILDREN WITH TUBERCULOSIS. F. RAGAZZINI, Riv. clin. pediat. **45**:473 (Aug.) 1947.

The author studied the behavior of serum calcium and of the inorganic phosphorus of the blood in 14 cases of tuberculosis in children after treatment with massive doses of vitamin D_2 and with or without intravenous administration of calcium.

There was in all the children a more or less pronounced increase in the calcium of the blood, which generally reached its maximum level between the second and fourth days of treatment. In those children to whom calcium was also given intravenously, the increase in the blood calcium level was more pronounced and of more prolonged duration.

There also was an increase in the inorganic phosphorus of the blood which corresponded chronologically to the maximum blood calcium level. In every child these changes were of transitory character.

FROM THE AUTHOR'S SUMMARY.

Diseases of Blood, Heart and Blood Vessels and Spleen

CONGENITAL PULMONARY STENOSIS WITH CLOSED INTERVENTRICULAR SEPTUM. S. H. AUERBACH and H. T. HARPER, Am. Heart J. **34**:131 (July) 1947.

The authors report a case of congenital pulmonary stenosis with an open foramen ovale but with no defect of the interventricular septum. The patient lived to the age of 20 years and showed signs of circulatory deficiency during only the last two and one-half years of life. During this period cyanosis and slight clubbing

of the fingers became obvious. The red blood cell count and hemoglobin concentration were moderately elevated. The authors emphasized the rarity of congenital pulmonary stenosis unassociated with a defect of the interventricular septum.

GIBSON, Chicago.

FAMILIAL CONGENITAL COMPLETE A-V HEART BLOCK. M. H. WENDKOS and R. S. STUDY, Am. Heart J. **34**:138 (July) 1947.

The authors report the presence of congenital complete auriculoventricular heart block in 2 siblings. One child, examined at the age of 5 years, had been known to have a slow heart since the age of 2 years. The electrocardiogram showed complete auriculoventricular block with a ventricular rate of 60 per minute. The physical examination revealed no significant changes.

The second child lived three days. An electrocardiogram, obtained about thirty hours before death, showed complete auriculoventricular heart block with a ventricular rate of 50 per minute.

In neither case was there evidence of an associated interventricular septal defect, though such a defect is observed in the great majority of instances of congenital heart block.

GIBSON, Chicago.

Diseases of Nose, Throat and Ear

AURAL DISEASES OF INFANTS. E. GYÖRGY, Paediat. danub. **2**:160 (Aug.-Sept.) 1947.

In the first part of the article several aural diseases of infants, as catarrh of the tube and of the mucous membrane of the tympanic cavity, are discussed. Their symptoms can be divided into otologic (local) and pediatric (general) ones. Methods of medical and the eventual surgical treatment of each condition are dealt with separately.

Otitis is a common disease in the newborn. Its frequency amounts, according to statistical data, to 5 per cent. Its symptoms are enumerated in detail and the author underlines the significance of the sequelae such conditions may have.

Otitis of infants with desquamative erythroderma (Leiner's disease) is dealt with extensively. Differentiation of this condition is necessary as, because of the increased sensitivity and secretion of the skin of the external auditory canal and of the epidermis of the drum, its pathogenesis varies from that of common otitis. In addition to this, the resistance of such patients is always decreased.

In the last paragraph, symptoms of initial otitis and mastoiditis are enumerated according to their pathogenetic and physiologic aspects. Then propagation of the infection from the tympanic cavity to the cells of the mastoid process and the pathologic changes of purulent mastoiditis are discussed.

FROM THE AUTHOR'S SUMMARY.

OTOGENIC BRAIN ABSCESS. L. B. W. JONGKEES, Acta oto-laryng. **35**:225 (May-June) 1947.

Sulfonamide drugs and penicillin have not particularly altered the course of a brain abscess when administered orally or intramuscularly.

The diagnosis of brain abscess may be easy if signs of increased intracranial pressure (headache, papilledema, slow pulse, paresis of the sixth nerve or specific alterations of the cerebrospinal fluid) and local signs pointing to the cerebellum or the temporal lobe are present. On the other hand, a large abscess can be present without any symptoms or localizing signs.

The composition of the cerebrospinal fluid seems to provide the best help for making a diagnosis, but some otologists fear to use a lumbar puncture for diagnostic purposes because the cerebellum may be crowded into the foramen magnum. Jongkees is of the opinion that the removal of a small amount of fluid is justified when the diagnosis is difficult.

The treatment of an otogenic abscess of the brain is surgical. Neurosurgeons prefer the extra-aural route, but otologists prefer the aural route because thereby the path of the infection may be traced. Some surgeons advise surgical intervention as soon as the diagnosis is made, while other prefer to wait four or five weeks until the abscess has been encapsulated. The danger of this procedure is that the patient may die while the capsule is forming. The type of surgical procedure varies greatly, but the general principle followed is extirpation of the abscess within its capsule or drainage.

Jongkees reports 2 cases of brain abscess, one of abscess of the cerebellum and one of abscess of the temporal lobe. In the last case recovery occurred after a conservative form of treatment, which consisted of puncturing the abscess, allowing the pus to escape through the needle and, then, introducing penicillin into the abscess through the puncture needle. In each of these cases the abscess complicated chronic otitis.

GROVE, Milwaukee, [ARCH. OTOLARYNG.]

Diseases of Lungs, Pleura and Mediastinium

EXPERIMENTAL IMMUNIZATION WITH THE VIRUS FROM PRIMARY ATYPICAL PNEUMONIA. MONROE D. EATON and WILLIAM VAN HERICK, J. Infect. Dis. **81**:116 (Sept.-Oct.) 1947.

Hamsters and cotton rats were immunized against the virus of primary atypical pneumonia by intranasal infection and by intraperitoneal inoculation of active and formalized virus.

Both hamsters and cotton rats developed virus-neutralizing antibodies after intranasal or intraperitoneal immunization, but the results indicated differences between these two species with respect to antibody titer and active immunity.

Attempts at passive immunization with hyperimmune rabbit serum were not successful.

TOOMEY, Cleveland.

THE TREATMENT OF ACUTE PRIMARY ATYPICAL PNEUMONIA, ETIOLOGY UNKNOWN. DAVID GREER, South. Med. J. **40**:881 (Nov.) 1947.

This is a complete discussion of acute primary atypical pneumonia. The importance of a roentgenologic study of the chest in establishing the diagnosis is emphasized. The value of the use of convalescent serum or commercial pooled blood is cited. A group of 45 children having atypical pneumonia is reported on, in which 1 or 2 units of liquid plasma was administered to each patient. The temperature fell to normal one to four days after such treatment was begun, and the cough and physical findings showed equally prompt improvement. The abnormal roentgenologic appearance, however, persisted two to four weeks.

LOGAN, Rochester, Minn.

TREATMENT OF EMPYEMA WITH INTRAPLEURAL ADMINISTRATION OF PENICILLIN. GALINA SOLOVEY and VICTOR PISCIOTANO, Arch. de pedia. d. Uruguay **9**:440 (Sept.) 1947.

The authors report the case of a 5 month old child in whom purulent pleurisy developed during a penicillin-treated pneumonia. Twenty-four hours following the intrapleural injection of penicillin, the pus became serosanguineous, and at forty-eight

hours aspiration yielded no fluid. Roentgenologic signs disappeared in seven days. The authors comment that, although there are differences in the reported statistics on the treatment of empyema by the local introduction of penicillin, there are many cases of favorable, even dramatic, results.

KALISKI, San Antonio, Texas.

BRONCHOPULMONARY MONILIASIS WITH LARYNGEAL INVOLVEMENT. JULIO MENEGHELLO and CARMEN AGUILO, Rev. chilena de pediat. **8**:578 (Aug.) 1947.

The authors report a case of severe moniliasis, produced by a mold fungus identified as Candida albicans in a girl 6 years of age, in which the etiologic agent was isolated in direct smear and culture from the larynx. The illness was unresponsive to the use of penicillin and sulfonamide drugs, but when potassium iodide was administered clinical improvement and regression of the roentgenologic findings were observed after fifteen days. A brief review of the literature accompanies the article.

KALISKI, San Antonio, Texas.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

INTRAPERITONEAL ADMINISTRATION OF SUCCINYLSULFATHIAZOLE AND PHTHALYLSULFATHIAZOLE. JOHN P. YOUNG JR. and WARREN H. COLE, Arch. Surg. **53**:182 (Aug.) 1946.

To find a more effective antibiotic agent in the treatment or prophylaxis of peritonitis caused by Escherichia coli, experiments were conducted with succinylsulfathiazole and phthalylsulfathiazole in dogs and in clinical tests in human beings.

In the dogs a sterile suspension of the drug in isotonic sodium chloride solution was injected into the peritoneal cavity. With a dose of 2.5 Gm. of succinylsulfathiazole per kilogram of body weight, there was no evidence of toxic reaction while in the case of phthalylsulfathiazole, an injection of 1 Gm. per kilogram of body weight could be used with safety.

In the clinical study a dose was adopted which would be no greater than 0.1 Gm. per kilogram of body weight. The two drugs were used in 51 patients about equally divided. The drug was dusted in as a powder or suspended in 20 to 30 cc. of isotonic sodium chloride solution and poured into the peritoneal cavity. No toxic reaction was observed in any of the patients with either of the two drugs. There were no abnormal urinary findings. No final evaluation of the clinical use of these drugs was made.

KAISER, Rochester, N. Y.

APPENDICITIS: A REVIEW OF NINE HUNDRED AND THIRTY-SIX CASES AT THE CINCINNATI GENERAL HOSPITAL. S. FASHIRO and M. M. ZINNINGER, Arch. Surg. **53**:545 (Nov.) 1946.

A careful analysis of all patients with appendicitis treated between Jan. 1, 1939 and Jan. 1, 1944 is reported. The results of this study are compared with two similar reports made on patients treated between 1915 and 1934 and 1934 and 1939. A number of significant facts is brought out in this survey. The incidence of chronic and interval appendicitis was greatly decreased in this five year period. Cathartics were employed by fewer patients in this period compared with earlier periods. The average delay in hospitalization in acute, unruptured appendicitis has been lessened. There has been a reduction in mortality from appendicitis attributed at least in part to an intensive educational campaign begun in 1934.

KAISER, Rochester, N. Y.

PATENT OMPHALOMESENTERIC DUCT AND ITS RELATION TO THE DIVERTICULUM OF MECKEL. C. FREDERICK KITTLE, HILGER P. JENKINS and LESTER R. DRAGSTEDT, Arch. Surg. **54**: 10 (Jan.) 1947.

A presentation of the history, embryologic, anatomic and pathologic factors, heterotopia, the relation to other congenital anomalies and the sex incidence of the diverticulum of Meckel is given. The relationship between it and the patent omphalomesenteric duct is discussed.

One hundred and two cases of patent omphalomesenteric duct and 26 additional cases in which prolapse of the intestine occurred through this structure were collected from the literature. These are briefly summarized. The clinical features, diagnosis and treatment of patent omphalomesenteric duct are discussed.

Operation for excision of the patent omphalomesenteric duct should be undertaken as soon as the condition is diagnosed to avoid the hazard of intestinal prolapse.

FROM THE AUTHORS' ABSTRACT.

CONGENITAL HYPERTROPHIC PYLORIC STENOSIS. CLEON A. NAFE, Arch. Surg. **54**:555 (May) 1947.

The author reports a series of 129 patients operated on for congenital hypertrophic pyloric stenosis with 2 deaths. The well known diagnostic procedures are discussed and the surgical technic is described in detail. It is pointed out that heredity is an important etiologic factor, as indicated by the frequency with which more than one case has occurred in the same family. Little emphasis is placed on the need for roentgenologic examination. It is stressed that the preoperative and postoperative management should be entrusted to a competent pediatrician.

KAISER, Rochester, N. Y.

VITAL STUDIES ON THE ETIOLOGY OF EPIDEMIC DIARRHEA OF THE NEWBORN. GEORGE MEIKLEJOHN, California Med. **67**:238 (Oct.) 1947.

An agent which causes keratitis in rabbits has been demonstrated in the rectal washings of 82 per cent of 45 cases of epidemic diarrhea of the newborn. The agent passes bacteria-retaining filters, can be passed in the rabbit cornea or the chick embryo and is presumably a virus.

Conclusive evidence that the virus is the cause of the disease has not yet been obtained.

PRYOR, Redwood City, Calif.

A CASE OF ESOPHAGEAL FOREIGN BODY WITH MEDIASTINITIS AND OTHER COMPLICATIONS. EDWARD H. LYMAN, Laryngoscope **57**:400 (June) 1947.

It is recognized that a foreign body in the esophagus is a dangerous condition. There have been many fatalities due to impaction, instrumentation for removal or complications caused by the body's piercing or eroding the esophageal wall. In the case herein reported, the foreign body pierced the esophageal wall with resulting mediastinitis, subcutaneous emphysema and other complications.

Several authors have reported cures obtained with the aid of massive doses of penicillin. Such doses were used in this case, together, of course, with the removal of the foreign body and other therapeutic measures. Lyman is of the opinion that the determining factor in the patient's ultimate recovery was the use of massive doses of penicillin. The case is reported in detail.

HITSCHLER, Philadelphia. [ARCH. OTOLARYG.]

THREE CASES OF PANCREATIC CYSTIC FIBROSIS. F. TREMBATH, Clin. Rep. Adelaide Children's Hosp. **1**:31 (May) 1947.

Trembath discusses 3 cases of fibrocystic disease of the pancreas. One of the cases was of a 3 day old infant who died soon after admission, apparently of meconium ileus due to lack of pancreatic secretion. Emphasis is laid on the use of duodenal intubation and aspiration as a diagnostic measure, and the technic is described.

McGUIGAN, Evanston, Ill.

THE PARASYMPATHETIC FACTOR IN MEGACOLON. JOSEPH LANNON, South African M. J. **21**:48 (July 12) 1947.

Lannon discusses a theory that megacolon is produced by parasympathetic underaction rather than by sympathetic overaction. He presents anatomic and therapeutic evidence to support this theory. The beneficial result of sympathectomy is considered to be due only to increase in the blood supply to the colon. Evidence of successful treatment with parasympathomimetic drugs is reviewed.

McGUIGAN, Evanston, Ill.

CAROB FLOUR AND ITS ANTIDYSPEPTIC PROPERTIES. ANDREINA VIANELLO, Lattante **18**:282 (May) 1947.

A flour made from the carob bean (the seed of the locust tree, *ceratonia siliqua*) and sold under the commercial name arobon® was used in the treatment of diarrhea in the Pediatric Clinic of Bologna, Italy, with favorable results. This flour contains 4.5 per cent protein, 1 per cent fat, 40 per cent soluble carbohydrates and 1.5 per cent pectin. The patients were first given a 5 or 10 per cent gruel of the flour. Then, the gruel was added to a milk formula. Rice water was substituted for the carob flour (farina di carrube) when the symptoms were relieved.

HIGGINS, Boston.

CHRONIC SCLEROSING HEPATITIS: REPORT OF TWO CASES OF CHILDREN. M. SACCA and A. ZANINI, Pediatria **55**:292 (April-June) 1947.

Two cases of chronic cirrhosis of the liver in children, 2 and 4 years of age, are reported. Exploratory laparotomy was done in each case and hepatic tissue obtained for histologic study. One case had an acute and the other an insidious onset. In the authors' opinion, the cirrhosis was biliary in origin.

HIGGINS, Boston.

Nervous Diseases

THE TREATMENT OF INFLUENZAL MENINGITIS. E. B. SIMS, Clin. Rep. Adelaide Children's Hosp. **1**:7 (May) 1947.

Sims reports on a series of 17 cases of influenzal meningitis treated in a period of three years. Two were of a single child, who had a second attack or a relapse eleven months after recovery. Two deaths and 15 recoveries resulted. The 2 children who died one 2 months and the other 13 months of age, had been ill for two weeks and two months, respectively, when admitted. Two children recovered on receiving sulfadiazine alone, 5 on sulfadiazine plus specific rabbit antiserums, 1 on sulfadiazine and penicillin and 7 on sulfadiazine, serum and penicillin.

The author points out that prior to 1944 the mortality from this disease in his hospital was 100 per cent, and he expresses his belief that, while no comparison of the various therapeutic measures can be made, the results in this series are unusually good.

McGUIGAN, Evanston, Ill.

ENCEPHALOPATHIES IN CHILDREN FOLLOWING BURNS. M. SCHACHTER, Ann. pædiat. **168**:105 (Feb.) 1947.

This is a report of 2 cases of encephalopathy after burns in which other predisposing factors could be recognized. Trauma to the brain at birth, parental alcoholism and infection play a part. Only on the site of previous damage to the nervous system can burns act as provoking factors. There is a discussion of several similar cases which have already been published.

FROM THE AUTHOR'S SUMMARY.

Psychology and Psychiatry

MENTAL ASPECTS OF GROWTH AND HEALTH. BERT I. BEVERLY, Illinois M. J. **92**:341 (Dec.) 1947.

In this discussion, Beverly calls attention to the fact that the problem in the care of the child from the point of view of mental health is to recognize and respect his inborn characteristics and the rate at which they develop in him and to satisfy his growth needs in order that he may reach his fullest capabilities. Since habit formation begins at birth, the younger the child the more important it is to supply his growth needs and keep him on the path which leads to mental health.

For bodily growth, a person requires adequate food and physical care. For mental growth, he needs security, an opportunity to grow according to his innate pattern and to take responsibility appropriate to his age and ability and, finally, freedom from standards of behavior beyond his developmental level. Of these things which are essential to mental health the most important is security.

BARBOUR, Peoria, Ill.

THE PSYCHOLOGICAL APPRAISAL OF CHILDREN WITH NEUROLOGICAL DEFECTS. E. MEYER and M. SIMMEL, J. Abnorm. & Social Psychol. **42**:193 (April) 1947.

Meyer and Simmel are of the opinion that the psychologic examination of children with neurologic disorders must be qualitative and descriptive in order to become meaningful for differential diagnosis, as well as for prognosis and therapy. The prevailing quantitative test methods should be supplemented by an orientation and/or by procedures based on genetic studies of reasoning and attention. Three groups of patients are discussed: 1. Children with impairment since birth who are predominantly characterized by a lag in development of the processes of abstraction. The typical psychometric picture is that of superiority of performance items over verbal items. In the field of performance, they are at their best with simple form board items. 2. Children who have apparently developed normally up to the time they had a severe injury or disease. These children show a discrepancy between their present inadequate level of functioning and the level of achievement attained prior to the impairment. Children with a severe head injury or rapidly developing neoplasm have a stock of information acquired prior to the acute insult which is almost completely intact and is easily activated under certain conditions. They have serious difficulties in reasoning and learning. In the group recovering from encephalitis the basic defects are essentially the same, but their ability to learn is impaired even more seriously by lack of concentration of attention. 3. Children with recurring seizure-like states, who periodically experience loss of effective

contact with the environment. The distinctive feature is the periodic fluctuation in the quality of the child's performance during a given examination or between examinations given at varying intervals.

FRANKEL, Philadelphia [Arch. Neurol. & Psychiat.]

SUPPLEMENT TO THE THEORY OF A LATENCY PERIOD IN SEXUAL DEVELOPMENT. IMRE HERMANN, Paediat. danub. **2**:17 (Nov.) 1947.

Freud's theory of the sexuality of the child can be based on comparative biologic facts. The latency period is a relative latency and not an absolute one, as many critics have said. Endocrinologic investigations show the truth of Freud's theory. The explanation for the cause of latency can be founded on the anthropologic hypothesis of giant human ancestors.

FROM THE AUTHOR'S SUMMARY.

Diseases of the Genitourinary Tract

LEIOMYOMA OF THE KIDNEY. I. CHARLES ZUCKERMAN, DAVID KERSHNER, BERNARD D. LAYTNER and DANIEL KIRSCHL, Ann. Surg. **126**:220 (Aug.) 1947.

Leiomyomas of the kidney in persons of the older age groups have been reported on rare occasions. This case reported by the authors is the first one recorded of large solitary leiomyoma of the kidney in a newborn child.

These tumors have the consistency of hard rubber and, on section, present a smooth, white, glistening appearance. They are usually well circumscribed and enclosed in a fibrous capsule. They grow slowly and present few signs other than presence of a mass and occasional pain and discomfort. The tumors have previously been detected in persons of the age group of 15 to 71 years and by far the greater number have been found in women.

The treatment of this condition is nephrectomy. In the absence of malignant changes the prognosis is good, and if malignant change does occur, there seems to be little tendency toward invasion of surrounding tissues.

The authors report this case in detail and discuss the histogenesis of the condition.

BANTIN, Omaha.

A GIANT URETERAL STONE IN A THREE-YEAR-OLD CHILD. HAMILTON W. MCKAY and H. HAYNES BAIRD, South. M. J. **40**:891 (Nov.) 1947.

A case is reported of a 3 year old boy who was found to have a ureteral stone 8 cm. in length. This was successfully removed at operation. It is said to be the largest ureteral stone in a child of this age ever reported. The patient had had poliomyelitis at the age of 2 years, as the result of which he was completely paralyzed in both lower extremities for several months. This period of immobility was, in the authors' opinion, etiologically responsible for the stone.

LOGAN, Rochester, Minn.

THE PLASMA VOLUME IN NEPHRITIS. PATRICK MACARTHUR, Arch. Dis. Childhood **21**:235 (Dec.) 1946.

The plasma volume was estimated in various types of nephritis; twenty-five estimations were made in acute nephritis, seventeen in nephrotic nephritis, eleven in chronic hemorrhagic nephritis and five in nephrosclerosis.

In acute nephritis, in nephrotic nephritis and in chronic hemorrhagic nephritis, alterations in the blood and plasma volumes were found. In acute nephritis the plasma volume was considerably reduced during the stage of diuresis and subsiding edema. In nephrotic nephritis the plasma volume was below normal during the stage of increasing edema and was considerably above normal during the stage of diuresis, diminishing edema and recovery.

It is suggested that in acute nephritis alterations in the volume of fluid excreted by the kidneys are the cause of changes in the plasma volume, but that in nephrotic nephritis changes in the plasma volume determine the volume of renal excretion.

In chronic hemorrhagic nephritis there is a low blood volume which is due to reduction in the total volume of circulating red cells. KELLY, Milwaukee.

TREATMENT OF PYURIA IN INFANCY WITH SULFONAMIDE DRUGS. PAUL ANSIAUX, Acta pædiat. belg. **1**:87, 1946-1947.

The first part of the article deals with a general discussion of nomenclature, definition, causation, course and various methods of treatment employed for pyuria. None of the methods has proved satisfactory. The author then describes the cases of his 11 patients whom he treated with sulfacetimide, sulfapyridine and sulfathiazole. He used 0.2 to 0.25 Gm. per kilogram of body weight (about ¼ grain per pound) for four days and then decreased the dose. Pyuria had disappeared completely in about twelve days. The Escherichia coli (present on culture in all cases) disappeared even earlier. The last part of the paper brings references from the literature to the work of other authors who had reached similar favorable conclusions as to the efficacy of this treatment. GLASER, Chicago.

Diseases of the Ductless Glands: Endocrinology

EFFECTS OF CASTRATION AND TREATMENT WITH SEX STEROIDS ON THE SYNTHESIS OF SERUM CHOLINESTERASE IN THE RAT. JOHN W. EVERETT and CHARLES H. SAWYER, Endocrinology **39**:323 (Nov.) 1946.

It is known that, while female rat livers contain five to eight times as much cholinesterase as male livers, ovariectomy results in a lowering of the enzyme content in the female to a value somewhat above that demonstrated in normal males. Orchidectomy, on the other hand, is said to result in a slight elevation. Further information on this subject is obtained from the experiments here reported which make it apparent that the sex difference in serum nonspecific cholinesterase in intact rats is the result of at least two factors. In the absence of effective amounts of androgen in the female, the estrogen causes an elevation of the enzyme to high levels. In the male, androgen acts to maintain a low serum esterase level, either by inhibiting the mechanism responsible for enzyme production or by increasing the rate of its removal. This it can accomplish even in the presence of estrogen. Progestin appears to have neither inhibitory nor synergistic effects with respect to estrogen in the elevation of the serum enzyme. JACOBSEN, Buffalo.

PITUITARY-ADRENAL CORTICAL CONTROL OF LYMPHOCYTE STRUCTURE AND FUNCTION AS REVEALED BY EXPERIMENTAL X-RADIATION. THOMAS F. DOUGHERTY and ABRAHAM WHITE, Endocrinology **39**:370 (Dec.) 1946.

The number of circulating lymphocytes is dependent on at least two major factors: the rate of delivery of lymphocytes from the sites of their synthesis and the rate of peripheral removal of these cells.

One of the important regulators of the rate of delivery of lymphocytes to the circulation is pituitary–adrenal cortical secretion. Moreover, it has been demonstrated that only those adrenal cortical steroids oxygenated in position 11 of the steroid nucleus exert this controlling influence. The lymphopenic effect of adrenal cortical steroids is a reflection of lymphocyte dissolution in lymphoid organs. Conversely, the lymphocytosis of adrenalectomized animals is probably due to the absence of the hormonal mechanism normally controlling lymphocyte dissolution.

The data here presented suggest that roentgen rays, unlike a wide variety of unrelated physical and chemical stimuli which cause dissolution of lymphoid tissue, do not depend on adrenal cortical mediation for their lymphocytolytic action. The lymphopenia seen in hypophysectomized, irradiated rats would suggest that pituitary mediation, whether via the adrenal cortex or the other endocrine glands, is not required for the involution of lymphoid tissue produced by roentgen rays. It is recognized that other agents may exist, which, if administered in suitable concentration, might also produce lymphocyte dissolution in the absence of the pituitary or the adrenal glands.

The normal dissolution of lymphocytes which occurs continually in lymphoid structures results in the release of serum globulin to the circulation. One of the proteins of lymphocytes is identical with normal serum gamma globulin, and the rate of release of this protein from lymphocytes is under control of the pituitary gland and the adrenal cortex. Consequently, any stimulus which augments pituitary–adrenal cortical secretion may produce an increase in the concentration of the globulin fraction of the serum proteins. Large doses of radiation, producing an extensive degeneration of lymphocytes in normal or adrenalectomized animals, therefore, also produce an increase in serum globulins. This response in adrenalectomized animals supports the working hypothesis that dissolution of lymphocytes is the mechanism by which these cells release protein to the circulation. The serum protein changes again indicate that the smaller degree of radiation (10 r) is acting as a nonspecific stimulant and producing its major effects on structure and function of lymphoid tissue by way of pituitary–adrenal cortical mechanism.

JACOBSEN, Buffalo.

THE DISTRIBUTION OF THE FEULGEN AND 2,4-DINITROPHENYLHYDRAZINE REACTIONS IN NORMAL, CASTRATED, ADRENALECTOMIZED AND HORMONALLY TREATED RATS. S. ALBERT and C. P. LEBLOND, Endocrinology **39**:386 (Dec.) 1946.

Bennett (1940) introduced phenylhydrazine hydrochloride as a reagent for the histochemical study of the adrenal cortex. A yellow reaction was observed which he attributed to the presence of ketonic lipids, presumably the ketosteroids elaborated by the gland. Later, the same reaction was observed in the interstitial cells of the testis, in the thecal and luteal cells of the ovary and in the syncytial layer of the placenta, presumably indicating the presence of the specific ketosteroids produced by these organs.

Gomori (1942) criticized the specificity of Bennett's reaction and emphasized that the adrenal glands, as well as sections from different kinds of necrobiotic tissues (tubercles, infarcts, tumors), reacted not only with phenylhydrazine but also with Feulgen's leucofuchsin reagent as used in the plasmal reaction. This reaction is stated to identify in tissue sections a group of substances named "plasmalogens," which comprise acetals of fatty aldehydes (such as stearic and palmitic aldehydes) bound with colamine glycerophosphate. Gomori was of the opinion that Bennett's reaction was due to plasmalogens rather than to ketosteroids.

As a result of the experiments here reported, the authors came to the conclusion that two types of substances may be considered as causing these reactions: keto-

steroids and plasmalogens. The persistence of the reactions after ablation of the two known sources of ketosteroids in the male rat, namely, the testes and the adrenal glands, runs counter to the first hypothesis, as does inability of progesterone and testosterone to react extensively with Feulgen reagent in vitro. On the other hand, the increase of both reactions with mercuric bichloride suggests that plasmalogens are the effective agents.

JACOBSEN, Buffalo.

Diseases of the Muscles, Bones, Joints and Lymph Glands

ACUTE OSTEOMYELITIS TREATED BY PENICILLIN. D. G. MCKAY, Clin. Rep. Adelaide Children's Hosp. **1**:16 (May) 1947.

McKay presents a series of 20 cases of osteomyelitis. He recommends the use of 20,000 units of penicillin every two hours in the early stages, with 15,000 units every three hours after the acute state, until 2,000,000 units has been given. The average patient was acutely ill and toxic for four days. Surgical treatment was confined to removal of sequestrums or drainage of residual abscesses late in the disease. The average stay in hospital was fifty days, and treatment following discharge was rarely necessary. Fifteen cases required no surgical intervention.

MCGUIGAN, Evanston, Ill.

VARIATIONS IN THE BLOOD PHOSPHORUS LEVELS (INORGANIC, LIPID AND TOTAL) IN THREE CASES OF PROGRESSIVE MUSCULAR DYSTROPHY AFTER INSULIN STIMULATION. L. NASSI and F. RAGAZZINI, Lattante **18**:155 (March) 1947.

The inorganic phosphorus level of the blood serum was observed to increase from approximately 4 to 8 mg. per hundred cubic centimeters two to three hours after the injection of 5 units of insulin in 3 children with progressive muscular dystrophy. Since insulin in normal persons decreases the inorganic phosphorus content of the blood, Nassi and Ragazzini tried giving injections of organic phosphorus to these same patients and obtained noteworthy clinical improvement.

HIGGINS, Boston.

MYELOPLAXOMA OF THE CERVICAL VERTEBRAE IN A TWO AND ONE-HALF YEAR OLD CHILD TREATED BY ROENTGEN THERAPY. D. AGOSTO, Lattante **18**:287 (May) 1947.

This patient had stiffness of the neck and muscle weakness in all four extremities. The abdominal reflexes were absent, while the arm and leg reflexes were greatly exaggerated. A roentgenogram showed a tumor anterior to the bodies of the third and fourth cervical vertebrae. A specimen taken for biopsy revealed a giant cell tumor characterized by many myeloplaxes. Relief of symptoms followed roentgen therapy. When the child was examined two and one-half years later, the tumor had disappeared and the child was perfectly normal.

HIGGINS, Boston.

ACUTE PRIMARY HEMATOGENOUS OSTEOMYELITIS OF THE OS PUBIS, TREATED AND CURED WITH PENICILLIN. N. DE ANGELIS, Pediat. del med. pract. **22**:22 (Jan.) 1947.

A 12 year old boy had a blood culture positive for hemolytic staphylococci and clinical signs and symptoms and roentgenologic appearance of osteomyelitis

of the os pubis. Treatment with sulfanilamide and sulfapyridine for five days was without benefit. Then a supply of penicillin was obtained, and 800,000 units was given over eleven days. Recovery was complete without sequestration.

HIGGINS, Boston.

EARLY FORM OF INFANTILE MYOPATHY SIMULATING HOFFMANN-WERDNIG SYNDROME (HEREDITARY FAMILIAL SPINAL MUSCULAR ATROPHY). R. DUBOIS, M. GRAFFAR and R. LEY, Acta pædiat. belg. **1**:1, 1946-1947.

A short description introduces the reader to the subject. Oppenheim's disease (amytonia congenita) is a congenital, nonhereditary, muscular atrophy with diminished or absent electrical reaction from which the patients recover. Hoffmann-Werdnig disease is hereditary, occurs between the sixth and tenth months of life, shows degenerative or absent electrical reaction and leads to death before the fifth year. Practically, the differentiation is so difficult that several authors have expressed the belief that the two diseases are one entity. The differentiation of these conditions from other myopathies is generally simple: the latter occur later in life and are often accompanied with pseudohypertrophy. The reflexes disappear only after atrophy has progressed. The involvement of the face is characteristic of myopathies, whereas the involvement of the trunk and abdomen seems to indicate the Hoffmann-Werdnig-Oppenheim disease. Muscular fibrillations speak for Hoffmann-Werdnig disease according to Ford, a fact with which the present authors disagree.

A case report follows: A child with a negative family history, who was normal up to the sixth month of life, showed muscular weakness, flabbiness and muscle fibrillation. He died of pneumonia at 5 years of age. Autopsy revealed severe atrophy of the muscle fibers, with replacement by fibrous and fatty tissue, and intact nervous tissue. These observations clearly classify the case in the myopathies. The characteristic feature of the Hoffmann-Werdnig-Oppenheim disease is the muscular atrophy by fields. The affected bundles correspond to degenerated anterior horn cells.

GLASER, Chicago.

Diseases of the Eye

SPONGIOBLASTOMA OF THE OPTIC CHIASM IN AN INFANT. J. SZUTRÉLY, Paediat. danub. **1**:237 (April) 1947.

A tumor of the brain was diagnosed in an infant 18 weeks of age. He had bilateral exophthalmos, edema of the papillae and hydrocephalus. The protein content of the cerebrospinal fluid was found to be increased, along with the value for serum cholesterol. The infant died from purulent meningitis and pneumonia. The autopsy confirmed the diagnosis and disclosed a spongioblastoma of the optic chiasm and nerve.

Both the age of the patient and the rare site of the tumor present some interest. According to clinical and pathologic statistics, about 75 per cent of the neoplasms of the brain in infants and children are gliomas. The age of the patient suggested intrauterine origin.

It is difficult to establish in infants a correct diagnosis in similar cases, as the elasticity of the skull may long compensate the intracranial pressure so that symptoms are likely to arise only quite late. Signs common in adults, like vomiting, vertigo and headaches, are difficult to evaluate in infants. Ventriculography is the most valuable aid to diagnosis, but it is useful only in those instances in

which the shape of the ventricles is altered by the disproportion due to increased pressure. Changes of the cerebrospinal fluid are seldom characteristic.

In the first year of life, therapeutic measures are rarely of benefit.

FROM THE AUTHOR'S ABSTRACT.

NEUROBLASTOMA OF THE RETINA. M. RADNÓT, Paediat. danub. **1**:351 (June) 1947.

Twenty patients with retinoblastoma were observed at a hospital for ocular diseases between 1940 and 1944. The age of the patients was under 3 years; the youngest was an infant 2 months old. In 10 patients the tumor was bilateral. In 1 the condition was hereditary.

The first clinical manifestations were defective vision, a white reflex of the pupil or, sometimes, secondary inflammation due to necrosis of the tumor. The neoplasm increases the intraocular pressure and may even cause metastases in various organs.

Therapy consists in enucleation of the involved eye. If the disease is bilateral, the attempt can be made to save one eye by roentgen irradiation or diathermy.

Histologic examination revealed neuroepithelioma in 10 and malignant retinoblastoma in 9 infants. The sclera was perforated in 6 of the children.

FROM THE AUTHOR'S ABSTRACT.

Skin Diseases; Allergy

THE TREATMENT OF PERSONS WHO HAVE BRONCHIAL ASTHMA. ARTHUR T. LAIRD, Minnesota Med. **30**:386 (April) 1947.

This paper represents a practical review of the treatment of bronchial asthma. Although reference is made to persons of all ages, it is interesting to note that of the 126 cases studied, 31.7 per cent were in children under 10 years of age and 9.5 per cent in persons between 10 and 20 years of age. This shows that 40 per cent of the asthmatic patients were young persons. Therefore, the paper should be of interest to those caring for children and should be consulted for details.

STOESSER, Minneapolis.

PURPURA NECROTICA. J. H. SHELDON, Arch. Dis. Childhood **22**:7 (March) 1947.

Three cases are described of an illness which appears mainly, if not exclusively, to affect children. It begins with features typical of an attack of allergic purpura; the purpuric lesions are associated with necrosis of the affected tissues, and healing is accompanied with separation of the resulting sloughs. These vary in severity from necrosis of the superficial layers of the skin to lesions penetrating deep into the underlying muscles, resulting in severe and permanent scarring. It is suggested that the disease may be connected with the Shwartzman phenomenon, and that in the early stages it may be characterized by short, critical phases during which the operation of slight but continued pressure may determine areas subsequently to be the site of deep necrosis. The illness leaves no sequelae apart from the scarring.

KELLY, Milwaukee.

COLD SWEATING, HYPOGLYCAEMIA, AND CARBOHYDRATE INSUFFICIENCY. J. L. EMERY, Arch. Dis. Childhood **22**:34 (March) 1947.

Cold sweating often follows the lowering of the blood sugar by insulin (after a lag period of ten to twenty minutes). A similar cold sweating occurs spontaneously in patients with celiac disease, particularly after fasting. Cold sweating

following use of insulin and occurring spontaneously is relieved by administration of glucose and diagonal epinephrine.

Children with celiac disease are particularly prone to cold sweating, but their fasting blood sugar levels are at least as high as normal. Cold sweating is not dependent on any actual level of the blood sugar. It is suggested that cold sweating in children with celiac disease, and also possibly in other ill children, may often be due to acute carbohydrate insufficiency independent of the blood sugar level. It is suggested that ill children liable to cold sweating should be given frequent feedings day and night.

KELLY, Milwaukee.

ICHTHYOSIS TREATED WITH STILBOESTROL. J. HELMAN, South African M. J. **21**:852 (Nov. 22) 1947.

It has been suggested that in ichthyosis the beta component of the thyroid proteins was deficient and further that perhaps castration increased this component. On this theory Helman treated a case of ichthyosis in a 12 year old boy with diethyl stilbestrol for a period of seven weeks. Improvement was notable and rapid. No complications were noted. Thyroid therapy for two months had failed to produce any improvement.

McGUIGAN, Evanston, Ill.

ALLERGIC NATURE OF THE ERYTHEMA NODOSUM PRODUCED BY SULFATHIAZOLE. H. BRIEGER, Arch. f. Kinderh. **133**:166 (April) 1947.

In erythema nodosum a characteristic hemogram was found: increased total number of leukocytes and an increased absolute number of granulocytes, with a compensatory reduction of the lymphocytes. The course of the hemogram is independent of the cause of the erythema nodosum. In a considerable number of children with early tuberculosis, even during the period before the cutaneous reaction to tuberculin became positive, it was possible to produce an erythema nodosum by giving oral doses of sulfathiazole. When sulfathiazole is given, the sedimentation rate is greatly increased during the stage of the eruption of the nodules of erythema nodosum. The hemogram observed during the time the eruption is developing after oral doses of sulfathiazole is similar to that described by the author as caused by a "secondary sulfonamide reaction." Probably, both reactions are of allergic nature.

In one child with a positive cutaneous reaction to tuberculin after doses of sulfathiazole, a phlyctenular conjunctivitis developed. This was regarded as an equivalent to the erythema nodosum, since the hemogram showed the same characteristics as seen in the condition resulting from sulfathiazole.

The author assumes that the thiazole ring of the sulfonamide compound is a causative agent participating in the production of the "isomorphous irritating effect" on the skin.

ARON, Chicago.

Surgery and Orthopedics

TIME OF ELECTION FOR ABDOMINAL SURGERY IN CHILDHOOD. EDWARD J. DONOVAN, New England J. Med. **236**:937 (June 19) 1947.

With stress on the necessity for early diagnosis and preoperative hydration, the conditions requiring abdominal surgical procedures are discussed in chronologic order, starting with hernia into the umbilical cord, stenosis of the esophagus, diaphragmatic hernia, atresia of the bile ducts, pyloric stenosis and congenital

obstructions of the duodenum and other parts of the intestinal tract requiring early surgical treatment. Disorders which occur later, intussusception, appendicitis, Meckel's diverticulum and hernias, are also included. GENGENBACH, Denver.

CONGENITAL LUXATION OF THE SUPERIOR EPIPHYSIS OF THE RADIUS. M. MOLTEDO, Arch. argent. de pediat. **27**:150 (March) 1947.

The author explains this luxation on the basis of an abnormal shortness of the ulna. This explanation agrees with the hypothesis of Ombrédanne. The Kline reaction was positive (2 plus), so that the author feels that the cause of the lesion is an innate syphilis.

ROJAS, Boston.

Miscellaneous

DEVELOPMENT AND USE OF BAL: A REVIEW, WITH PARTICULAR REFERENCE TO ARSENICAL DERMATITIS. MARION B. SULZBERGER and RUDOLF L. BAER, J. A. M. A. **133**:293 (Feb. 1) 1947.

The work of Peters, Stocken and Thompson established that simple synthetic dithiol compounds forming stable nontoxic compounds with arsenic have greater affinity for arsenic than the monothiol or "dithiol" proteins of tissues. This led to the discovery of 2,3-dimercaptopropanol called "British antilewisite" or BAL.

Experimental work with BAL demonstrated that its local application could prevent cutaneous damage from arsenical vesicant agents or arrest and even reverse skin damage when applied within two hours after exposure to the agents. Systemic poisoning produced by arsenical compounds was counteracted. BAL has proved useful in treating the following complications of arsenic therapy: toxic encephalitis, granulocytopenia, jaundice, "arsenical fevers" and massive overdose of arsenical compounds. In 3 cases of aplastic anemia no beneficial results occurred. The following dosage is suggested: in severe cases 3 mg. per kilogram of body weight every four hours for twelve injections, then every six hours for four injections, then two injections daily for ten days. For less severe cases the dose is 2.5 mg. per kilogram of body weight. Toxic reactions occur when the dose reaches 4 or 5 mg. per kilogram but these have been of a temporary nature. They include nausea, vomiting, headache, burning sensations in the mucous membranes and extremities, lacrimation, salivation, muscular aches, feeling of constriction in the chest and elevation of blood pressure. Locally, BAL acts as a whealing agent.

BAIRD, Wauwatosa, Wis.

DIAGNOSTIC VALUE OF ELEMENTARY ELECTROMYOGRAPHY IN PEDIATRICS. R. TURPIN, J. LEFEBORE and J. LERIQUE, Presse méd. **54**:856 (Dec. 25) 1946.

Electromyography is of value in studying the course of generalized conditions, such as tetany or myasthenia. Since the electromyogram reflects the excitation state of the anterior horn cells, it can be used to measure the degree of damage in cases of hypotonia. Differential diagnosis can easily be made between neuropathic and myopathic atrophy.

DAFFINEE, Melrose, Mass.

Society Transactions

CHICAGO PEDIATRIC SOCIETY

John L. Reichert, M.D., *President*

Regular Meeting, Dec. 21, 1948

Streptomycin Used in Treatment of Pulmonary Tuberculosis in Children.
DR. EUGENE T. MCENERY.

This is a report on 21 cases of pulmonary tuberculosis in children treated with streptomycin and observed for a period of eight months to one year. The work was made possible through a grant from the board of the City of Chicago Municipal Tuberculosis Sanitarium.

Type of Patient Treated.—Of the 21 children, 18 were classified as having a progressive primary lesion. This type of lesion is of relatively recent origin, sometimes demonstrated on physical examination by impaired resonance and suppressed breath sounds, but usually manifesting no such change. Roentgenograms show a soft, infiltrative shadow, extending from the hilus to the periphery of the lung, with some enlargement of hilar shadows. Three children were classified as having a far advanced adult type of pulmonary tuberculosis, with activity and pulmonary cavities. These children had failed to respond to a regimen of rest in bed and pneumothorax and their conditions had been taking a downward course for one to two years.

Age of Patients.—Of the children with the progressive primary lesions, the ages varied from 8 months to 11 years. Those with the adult type were 11, 12 and 13 years of age, respectively. Of the 21 children, 15 were Negro and 6 were white. There were 9 boys and 13 girls.

Dosage of the Drug.—In the beginning of this study the majority of the children received 0.5 Gm. in divided doses daily (twice daily). This has now been decreased to 0.3 Gm. for all patients in one injection daily.

Duration of Treatment.—The majority of the patients received the drug for one hundred and twenty days: this has now been reduced to ninety days.

Toxic Manifestations.—With the smaller dosage, 0.3 Gm. once daily, toxic reactions have not occurred; no auditory or vestibular disturbance has been noted; no cutaneous reactions have been present.

Response to the Drug.—The clinical response has been the same in all the children; it has occurred within a week to ten days. The following reactions have been noted consistently: a drop in temperature, improvement in appetite, change in disposition and lessened irritability. The physical findings did not show much change for at least one month. The roentgenograms showed little improvement for three months.

Results.—One of the patients with a progressive primary lesion died from tuberculous meningitis six months after administration of streptomycin was stopped. One with the adult type of tuberculosis died with extensive pulmonary involvement; a second one is in serious condition, and the third is awaiting surgical treatment.

Sputum has been negative for the tuberculous organisms in all the patients except 4, 2 with the progressive primary type and 2 with the adult type of tuberculosis.

Conclusions.—From a study and follow-up observation a series of 21 cases of tuberculosis in children, I have drawn the following conclusions:

Streptomycin is a valuable drug for the treatment of active toxic progressive primary tuberculosis. It lessens the toxic manifestations of the disease. It has reversed the general stationary or downward course and slowly but constantly caused resorption of infiltrative processes, as demonstrated by physical findings and roentgenologic appearance. The most favorable results have been in those children with recent primary infiltration; this was demonstrated in 6 of the children under 2 years of age.

Streptomycin is not a cure-all; its use is still in the experimental stage and a larger number of cases will have to be observed over a longer period of time to make these conclusions confirmative.

DISCUSSION

DR. HENRY C. SWEANY: I am not in a position to discuss the details of the progress of these children and shall confine my remarks to the pathologic and bacteriologic phases. I should like to show lantern slides of the patient reported on by Dr. McEnery who had meningitis and died. Dr. McEnery showed the large mass of calcification from that patient which proved to be the entire middle lobe. The incision of the lung was made, the flap raised to show the underlying calcifying caseation. The rest of the lobe is a cavity in which are deposits of semicalcareous masses 2 to 3 mm. in diameter. The second slide shows a section through the various lesions of the lung; healed tubercles may be seen in the upper lobe of the left lung and masses which have become encapsulated and are on the way to healing in the lower lobe. There is a huge cavity which has been collapsed and is partly healed. In the base are two masses of caseous material becoming encapsulated and partly calcified. These two areas are undoubtedly reinfection processes from the primary focus in the middle lobe. The slides give an idea of the tremendous involvement of the lung.

The tubercle bacilli in this child probably developed resistance to streptomycin and nothing was gained in reinstituting treatment. The meningitis was of the simple basilar type; no tubercles were found elsewhere. Had it not been for the resistance we had a good chance to save the child from meningitis. This brings up the one discordant note in treatment with streptomycin—resistance of the bacilli to the drug. Otherwise, the results are mostly good.

This is the first drug that has shown definite inhibition or suppression of tubercle bacilli in the human body. How it acts no one has been able to prove, but it appears to involve the bacilli and prevent them from growing and, probably, in time kills them completely. In our work at the City of Chicago Municipal Tuberculosis Sanitarium my colleagues and I have many times observed patients who still had positive sputum on examination, but from which we were not able to grow cultures of the organism or to infect animals. Apparently, many of these acid-fast organisms were killed or so weakened that they were unable to infect animals. We now have a drug, therefore, that does something to inhibit the metabolism of the tubercle bacillus.

As to the type of pathologic change, with infiltrating lesions in which there are not too many bacilli the results are probably better than with any other type. When the disease has progressed to the stage where there are caseation and massive infiltrative processes, the results are not so good, whether because of the

number of bacilli present or the inability to penetrate the caseous mass is not known. Various other lesions in the body seem to respond; in old tuberculous sinuses and tracheobronchitis, few acid-fast organisms are present and a good response is obtained. There does seem to be a certain relationship between the number of bacilli and the result; there also seems to be a relationship between the physical character of the pulmonary lesion itself and the result. Where the lesion is easily accessible to the drug, the result is better than where there is much concentration of dead tissue and where the drug does not penetrate readily.

DR. GEORGE C. TURNER: I have been much interested in this group of cases. I should like to say a word concerning the dosage of streptomycin; Dr. McEnery used from 0.1 to 0.5 Gm. in twenty-four hours, or about 30 mg. per kilogram of body weight; this parallels the dosage my associates and I have used in adults.

We have now treated 750 patients with streptomycin for from sixty to one hundred and twenty days; any vestibular disturbance which has resulted has been of a passing nature. The dosage that we have used has been 0.5 to 0.75 Gm. We observed that the results from this smaller dose are the same as those obtained with larger doses. This is important in infants or children with a type of primary pulmonary tuberculosis from which spontaneous recovery is expected in a high percentage of cases. A large number of vestibular disabilities would limit use of streptomycin to those patients in whom it was a matter of life or death.

By our present definition, treatment for children with streptomycin is indicated for (1) all those with hematogenous dissemination, pulmonary miliary and generalized miliary tuberculosis and tuberculous meningitis; (2) infants and young children showing active symptoms of tuberculous disease; (3) those of any age who have massive primary lesions, and (4) all those with pericarditis and tuberculous peritonitis.

With the recent development of less toxic forms of streptomycin, we will, in the future, have to consider using this drug for all children with primary tuberculosis to kill as many organisms in the primary lesion as possible so as to decrease ultimately the number of late endogenous reinfections. This would be done in order to sterilize the latent foci, which are stated to be the source of much of the adult or reinfection type of tuberculosis.

This series is growing; we believe Dr. McEnery will have a more definite answer in the near future with our larger group of cases.

DR. ALFRED D. BIGGS: I want to show roentgenograms of an unusually interesting case which my associates and I followed at St. Luke's Hospital for six years; it was also followed at the City of Chicago Municipal Tuberculosis Sanitarium. The case illustrates that it is difficult at times to distinguish between the primary and the reinfection types of tuberculosis.

This boy was first seen by us in 1942, when he was 8 years old, at which time the picture shown was taken. He had been in Cook County Hospital and St. Luke's Hospital and at the Municipal Tuberculosis Dispensary. In these institutions a variety of diagnoses had been made: a destructive type of tuberculosis, atelectasis, foreign body and tumor. The product of one gastric washing at St. Luke's in 1942 injected into a guinea pig resulted in a tuberculous reaction. That year the patient was in the Municipal Sanitarium for ten months and was studied carefully from the standpoint of detecting organisms, but without success. He was discharged from the Municipal Sanitarium in 1943 with a diagnosis of primary tuberculosis; we concurred in that diagnosis. At that time it was also suggested that his condition might be Hodgkin's disease or lymphosarcoma. At the onset, in 1942, he apparently had had a cough, with production of sputum and fever, for a short time

On the basis of the roentgenogram taken in 1944 we felt certain his case was one of primary tuberculosis. We could have dismissed him then, but it is our custom to follow these cases for a long time. In 1945, his condition was worse; there was substantial increase in the size of the mass and, at this time, I thought we were dealing with a reinfection type of tuberculosis. In 1946, there was improvement and he still had no symptoms. He was perhaps a little worse in 1947, and a gastric washing revealed tubercle bacilli. It was felt at the Municipal Sanitarium that the reinfection type should be considered, although the diagnosis was not entirely justified. In February 1948, we could find no tubercle bacilli by gastric lavage. Dr. Clara Jacobson saw him in 1948 and expressed her opinion that a definite diagnosis was not justified but that the condition was probably a primary lesion.

This case illustrates the point that it is sometimes difficult to clarify the type of lesion. If one wishes to call it the reinfection type, there is roentgenologic evidence for that. On the other hand, if one wishes to consider it a primary lesion, there is clinical evidence for that. The child has been well and has had no cough or any symptoms of tuberculosis since the early weeks of 1942. I do not know with certainty whether his tuberculosis is of primary or reinfection type.

DR. EUGENE T. MCENERY: With reference to the case cited by Dr. Biggs, it brings out the fact that many so-called primary lesions get along better when nothing is done. In the last slide he showed, there was calcification, and I should think, in looking at the series of plates, that there might be an acute process around the upper main bronchus which would produce atelectasis. I should consider a bronchoscopic examination to determine whether there is reinfection. The last roentgenogram looked satisfactory. Persons with primary infection apparently get well.

Recently, a physician from Latin America showed a beautiful study of a series of children; the illness in a number started as primary lesion and, in spite of good care, they began to cough and died. He said he could not predict whether a child was going to recover or die. If harm may result from giving streptomycin, I think we are taking a worth while chance. On the other hand, it is a mistake to do nothing in the hope of something better; it may become too late to start treatment with streptomycin. It may be possible to give surgical treatment; and I think the sooner the thoracic surgeons start operating on these children the better. Use of streptomycin, while it is not a cure, is certainly of benefit in tuberculosis.

Penicillin in Pediatrics. DR. B. M. KAGAN.

A study was made of the relative degrees of in vitro sensitivity to penicillin of various pathogenic bacteria. Different strains varied considerably in their sensitivity to the substance. The concentrations of penicillin obtained in the serum after varying dosages of the following forms per unit of body weight in infants and children are reported: crystalline penicillin G in isotonic sodium chloride solution given intramuscularly; the same form of penicillin in gelatin capsules and in suppositories of theobroma oil and white wax given rectally; crystalline sodium penicillin G in sesame oil given intramuscularly, and crystalline potassium penicillin G in a new type Romansky formula given intramuscularly. The last preparation, when given in doses of 4,000 units per pound maintained levels after twenty-four hours which were above the minimum concentration required to inhibit most strains of alpha and beta hemolytic streptococcus and of pneumococcus.

and the serum concentrations obtained with this preparation twelve hours after administration were equal to or above the minimum concentration required to inhibit most strains of hemolytic Staphylococcus aureus.

Analyzed statistically, there is little difference in the twenty-four hour concentrations of penicillin in the serum following intramuscular injection of 4,000 units per pound of crystalline procaine penicillin G in sesame oil and injection of the same dosage of crystalline potassium penicillin G in white wax and peanut oil (new Romansky formula). However, procaine penicillin in sesame oil was found superior to the preparation of white wax and peanut oil because it was accompanied with no local reactions, either symptomatic or objective, nor with any evidence of allergy which could be attributed to the change in the form of the drug or to the excipient.

When 8,000 units per pound of procaine penicillin in sesame oil was given, all the patients had serum penicillin concentrations of 0.04 unit per cubic centimeter or greater at the end of twenty-four hours (average 0.83 unit per cubic centimeter). When this dosage was given every twenty-four hours, there was no significant increase in the serum penicillin concentration at the end of each twenty-four hour period.

DISCUSSION

DR. JOHN A. BIGLER, Highland Park, Ill.: I want to compliment Dr. Kagan on this careful work. Anyone who has tried to determine penicillin levels in the laboratory knows that it is not easy. I agree with Dr. Kagan that the height of penicillin level is still on a theoretic basis. I do not think it is known as yet whether a constant level is necessary to achieve good results. More work must be done to ascertain whether or not the regular levels may not be satisfactory for treatment of most infections. From titrations my associates and I have done, it has not been uncommon from the same dosage in patients of the same size to have a high level at one time and a level of 0 at another time and still obtain a good therapeutic response. The problems of constant high levels and organism resistance have not been completely determined. Dr. Hand and I have been treating a great many of the infections seen in children with ordinary penicillin, given in doses of 100,000 units every twelve hours, with results that have been at least comparable with those in patients who had the same infections and were given penicillin every three hours. We were doing this because it was shown that there is a higher survival rate in rats with streptococcic infections on a twelve hour dosage schedule than in those on a three hour dosage schedule.

DR. B. M. KAGAN: The literature at present is not clear on the subject of intermittent and continuous therapy. Perhaps the question can best be answered by a review of the observations of the investigators whose work is being widely quoted by those who advocate the use of intermittent therapy. These investigators did excellent work so far as it went. They were, however, dealing in one series of experiments with a strain of streptococcus, organisms of which are usually sensitive to penicillin, and in another series with a strain of pneumococcus, organisms of which likewise are sensitive to penicillin. Furthermore, it has been shown that the majority of these organisms are killed quickly, within forty-five minutes to an hour. I do not wish in any way to belittle their excellent work, but, if they had shown the length of time required to kill the particular strains with which they were working, we should be in better position to draw conclusions from their observations. If mice are given an injection of a strain which is so sensitive to penicillin that it takes one hour or less to kill it and then are given

one large dose of sodium penicillin, it is reasonable to expect that a high percentage will recover. But we are not always dealing with such sensitive bacteria. If the investigators had repeated the experiments with more resistant organisms, we should have a more satisfactory basis on which to proceed with clinical experiments. We must expose the bacteria to the drug for a continuous period, as long as that required to kill them, and some bacteria require a long time, those of several strains as long as thirty-five hours.

Furthermore, it has been shown that the bacteria are killed during the phase when they are dividing, but that during their resting phase the drug does not kill them. If we are able to maintain continuous bactericidal levels in the blood, we are more likely to reach all the bacteria at whatever time they may be in their dividing phase. In the light of the known facts, I should say that much more fundamental work must be done before we can accept intermittent therapy for general clinical use.

About the waste penicillin, it has been shown by Eagle that, as the concentration of penicillin in the blood is increased beyond that at which there is optimum bactericidal activity, the drug becomes less instead of more effective.

We use a serial dilution technic. Once the procedure is set up determinations are not too difficult, but, as Dr. Bigler points out, it requires proper facilities and adequate personnel.

If increased doses are given, there will be a high concentration for a longer time, but not necessarily a significantly higher concentration within the first twelve hours. In order to obtain a higher concentration, two injections can be given at the same time, each in a different site; but it is probably better to reduce the interval between doses—in other words, to give the dose at twelve hour intervals instead of at twenty-four hour intervals. We feel it is not wise to depend on the presence of adequate serum concentrations at ninety-six hours. We have found some penicillin in the blood ninety-six hours after injection, but the concentration beyond the twenty-four hour period is not reliable and when present is only high enough to kill the more sensitive strains of bacteria. Even in special circumstances, when treating an infection due to the most sensitive of these bacteria, I should not depend on these preparations forty-eight hours after injection and should still prefer a twenty-four hour interval for dosage.

Streptomycin in Treatment of Whooping Cough. Dr. Harry Leichenger and Dr. Allen Schultz.

This study was undertaken to determine the effect of streptomycin on uncomplicated whooping cough. Only patients in either the catarrhal or the early paroxysmal stage of the disease were included. Before being assigned to a group, each patient was observed in the hospital for three days. A diagnosis of whooping cough was made only when the patient exhibited at least two of three diagnostic criteria: (1) cough plate positive for pertussis organisms; (2) leukocytosis with lymphocytosis, and (3) typical paroxysms of coughing.

On completion of the three day period of observation and with establishment of a diagnosis of whooping cough according to the aforementioned criteria, the patients were assigned in rotation to one of three groups; there were 8 patients in each group. Group I were the controls; they received the usual symptomatic treatment. Group II received 1 Gm. of streptomycin intramuscularly, divided into eight equal doses and given every three hours around the clock. Group III also received 1 Gm. of streptomycin, by the aerosol route. The streptomycin was dissolved in 8 cc. of isotonic sodium chloride solution and nebulized by attaching

a vaponefrin® nebulizer to a B-L-B inhalation mask. The rate of flow of oxygen was 4 to 5 liters per minute. The average period required to administer a dose was seven to ten minutes. Both forms of therapy were continued for seven days.

The patients were all observed in one ward. Nurses were assigned to this ward continuously, and it was their responsibility to time the duration of each paroxysm in seconds and to record the number for each patient. They also recorded any other phenomena, such as emesis, epistaxis, apnea, cyanosis or convulsions. These nurses had no other duties during the period of this study. Other nurses administered the usual nursing care.

Patients receiving streptomycin therapy experienced the greatest measure of benefit as determined by the number of paroxysms and their duration before therapy compared with the number and duration after therapy. Clinically, experienced observers also noted that patients receiving streptomycin did better than those not receiving the antibiotic substance. The aerosol group seemed to experience the greatest measure of benefit. There were no complications in the streptomycin group. In the control group there were complications, such as pneumonia and otitis media. One patient in the control group died of pneumonia.

DISCUSSION

DR. ARCHIBALD L. HOYNE: At Municipal Contagious Disease Hospital where patients with whooping cough only under 1 year of age are admitted, my associates and I have not treated many with streptomycin. My own impressions have not been exceedingly favorable in regard to such therapy. However, we have not had the same opportunity to try it out as has Dr. Leichenger. Another reason we have not used streptomycin more for whooping cough is that our fatality rate has been low. When there are few deaths, it is difficult to determine exactly what the value of a new remedy can be. For seventeen consecutive months we did not have a fatality among infants less than 1 year of age. If we had selected one particular remedy, we might have attributed our excellent results to that specific treatment. It seems to me that to disclose the real value of streptomycin for whooping cough it would have to be used for a large number of children with extremely severe attacks. In addition, we cannot overlook the possibility that streptomycin may do some harm; even in as short a time as a week, deafness has occurred, and, if hearing is completely lost, the probability is that the child will not regain it. In the case of an infant loss of hearing would be a calamity because the child would be not merely deaf but a deaf-mute. Consequently, we have not been strongly in favor of streptomycin for treatment of whooping cough in infants. Use of the drug may be justified in older children, but I think other factors are more important. Good ventilation and proper nursing care are fundamental; pertussis immune serum (human) N. N. R. is of value.

DR. HARRY LEICHENGER: I think the literature will soon contain more reports. We have seen a reference to some 150 cases from Willard Parker Hospital on this subject, and a recent article (Leichenger, H., and Schultz, A.: J. Pediat. **33**:552 [Nov.] 1948) reported the use of streptomycin in whooping cough. The authors found the aerosol route to be the one of choice.

I think Dr. Hoyne's criticisms are most pertinent. After hearing Dr. McEnery's reference to the use of streptomycin for one hundred and twenty days, one need not be reticent about using it for a week. We have revised our thinking as to the size of dosage, however, since the dihydrostreptomycin has become available. This can be used even more freely without any or with only a few side reactions.

Regular Meeting, Jan. 18, 1949

Epidermolysis Bullosa. DR. A. MATHESON.

This paper will be published in full in the November 1949? issue of the AMERICAN JOURNAL OF DISEASES OF CHILDREN.

DISCUSSION

DR. JAMES R. WEBSTER: Dr. Matheson described his cases with minute attention to detail and has reviewed the literature exhaustively. The work constitutes a valuable casuistic contribution to the field of pediatric dermatology.

During the past year my associates and I have seen a case at Children's Memorial Hospital which was in many respects, including the early death, similar to Dr. Matheson's first case. It differed chiefly in that the patient was a full term, fully developed infant weighing 6 pounds, 1 ounce (2,749.9 Gm.). A family history of similar trouble, or in fact of any developmental defect, was entirely lacking, and the possibility of consanguinity was, to say the least, remote in that the mother was an English war bride of an American soldier of Italian extraction.

The lesions were noted at birth. The baby was first seen in consultation by Dr. A. B. Falk and was then transferred to our hospital, where she died at the age of 16 days. Postmortem examination revealed disseminated bronchopneumonia, atelectases of the lungs and a Staphylococcus aureus meningitis, in spite of the fact that she had received both sulfonamide drugs and penicillin. This agrees with the observations in most instances of early death of some rather pronounced infectious phenomenon, for which the cutaneous lesions undoubtedly served as the portal of entry.

The cutaneous signs during life consisted of bullae up to 8 cm. in diameter, which ruptured easily, leaving large denuded areas on the feet, hands, face, buttocks and scalp and in the mouth. In spite of extremely careful handling many instances of a positive Nikolsky sign were observed.

The cause of epidermolysis bullosa certainly remains unknown beyond the fact that it is a congenital anomaly. I agree with Dr. Matheson that there is no basic difference between the congenital and the so-called acquired forms of the disease. I suspect that the tardive cases merely represent a milder form, usually of the simple type which manifests itself for the first time when more pronounced mechanical factors are encountered, as was observed in soldiers during World War II, especially in tropical climates.

The pathogenesis of the disorder is obscure; it seems that there may be a pathogenetic difference between the simple and the dystrophic forms. In the simple forms scarring does not occur unless there has been considerable secondary infection, whereas scarring is the rule in dystrophic cases. There is a correlation in this fact in that in the simple form of the disease the elastic tissue appears normal under the microscope, while in the dystrophic form abnormalities and even absence of elastic tissue have been noted by some observers. In the dystrophic form also there are changes referable to the epidermis and its appendages and the mucous membranes, and even in some cases to the nervous system, entirely analogous to those changes seen in instances of congenital ectodermal defect. Is it not, therefore, possible that in the simple form alone we are dealing with some congenital angioneurosis, trophoneurosis or polyglandular or toxic process, the manifestations of which are precipitated by trauma, and that in the dystrophic form, especially those cases showing recessive inheritance, there is added to this

a congenital defect involving elements of both mesodermal and ectodermal origin? Some interesting observations have been the frequent persistence of the thymus and the finding of elevated amounts of porphyrin in the urine, but the significance of such observations is still obscure.

Effects of Measles on Nephrotic Syndrome. DR. HERMAN B. LANDER.

During the recent epidemic of measles in the Chicago area in the winters of 1947 and 1948 my colleagues and I were privileged to observe the effects of the disease in 8 patients with the nephrotic syndrome. Seven of the patients were studied at the Children's Division of Cook County Hospital and 1 at Michael Reese Hospital, with the collaboration of the Hektoen Institute, the Kunstadter Laboratories of Pediatric Research and the Biochemistry Department of Michael Reese Hospital.

Though remissions in the nephrotic syndrome have been reported following many infections, they seem to have been most regularly noted during or following measles. The clinical picture of the nephrotic syndrome is studded with remissions and exacerbations. All our children were given high protein, low salt diets and received large doses of iron and vitamin preparations.

In our series of 8 patients with the nephrotic syndrome complicated by measles, 4 showed decided improvement, 3 had moderately good remissions and 1 had no response. On the basis of these results and the reports in the literature, there is little doubt that in some patients with the nephrotic syndrome a remission follows infection with measles. In our patients the results obtained did not seem dependent on the azotemia and hematuria present, as has been reported by other observers.

The nephrotic patient who acquires measles may be critically ill. Because of this and because the degree of remission may not be comparable with the severity of illness during measles, it is questionable whether it is wise deliberately to expose these patients to measles. The possible role of the gamma globulin fraction of the blood was discussed. Perhaps the low gamma globulin concentration in the blood is an important factor in the extreme susceptibility to infections that these patients show.

DISCUSSION

DR. HARRY H. BOYLE: Dr. Lander had a rare opportunity in being able to observe this number of patients with nephrotic syndrome at one time, particularly during a measles epidemic. We all know how few cases of chronic nephritis and nephrosis one sees in private practice. Dr. Lander's observations are accurate and a contribution to the literature. Two interesting questions arise in connection with measles and the nephrotic syndrome.

First, if there is a relation between antibody formation and diuresis, should we give these children human measles immune serum or globulin? The economic factor enters into such a practice, for the cost of either product would be great in the quantities required. Dr. Lander has indicated that he and his associates are doing more work along this line, and I hope they have the facilities for treatment of these patients in this manner.

The second question is even more important from the practical and clinical standpoint. Should we expose these children to or inoculate them with measles? Those who were at the Buffalo meeting of the American Academy of Pediatrics in April 1948 heard Dr. C. A. Janeway, of Boston, speak on the treatment of the nephrotic syndrome. He gave an excellent discussion of general treatment, stressing the points that we should try to prepare the parents for a long period of illness

and that often too much is attempted in the way of treatment. He discussed measles inoculation as a therapeutic measure and left the impression that fair results were being obtained. In a later personal communication he was not so enthusiastic, for several children who had shown improvement had had relapses. When I returned from the meeting, it was near the end of our measles epidemic but we attempted to expose two edematous children, both with nephrosis, to children with early, florid measles. Only one of them contracted measles and this child was free of edema within a few days. Soon afterward, the albumin disappeared from the urine and the boy appeared clinically well. Within a month he had albuminuria again, and at present is in about the same clinical condition as before he had measles.

My feeling is that we are not justified in giving a child measles as treatment of the nephrotic syndrome. Dr. Lander's observations appear to bear out this impression. One needs to see only 1 case of measles encephalitis or of any other serious complication of measles to realize that the end does not justify the means.

So far as general treatment of nephrotic syndrome is concerned, I have felt for some years that the child who does not respond with partial or complete diuresis to early treatment of any kind with serum, plasma, thyroid, infection, acid-ash diet or alkalis has a poor prognosis and will eventually die with chronic glomerulonephritis. Those children who have prompt diuresis with early treatment are those who will probably eventually recover, although the condition may persist for years.

To illustrate the effect of infection on the nephrotic syndrome, I wish to mention 2 cases briefly. These illustrate a point we have all known for years—that other infections besides measles have a favorable effect on the condition. The first is the case of the 3 year old boy who was exposed to measles and did not contract the disease. In November, fluid formed in one side of the boy's chest; several taps did not have any permanent effect and then Dr. W. J. Potts drained the thoracic cavity surgically. The fluid later became infected with a mixture of organisms and the patient was treated for several weeks with penicillin and streptomycin. After the infection in the chest cleared, the edema disappeared and the urine showed a negative reaction for albumin. A month later albumin appeared in the urine again and is still present. There is no edema. The other boy, 6 years old, had had nephrosis for about one year when he entered St. Luke's Hospital with peritonitis. After recovery from the abdominal infection, the edema disappeared and the urine became negative. At present, some six months later, the boy is clinically well.

In summary, it may be stated that we are probably not justified in giving measles to children as treatment of the nephrotic syndrome. Even though there is improvement it may be only temporary. On the other hand, the complications of measles must not be forgotten. We have all seen more children recover spontaneously from this condition than following measles.

DR. ARTHUR H. ROSENBLUM: I had the privilege of studying these patients with Dr. Lander on our service at the Children's Division of Cook County Hospital. I wish to point out that we did not deliberately expose any of these children to measles, but that measles appeared in the nephritic wards, which gave us the opportunity to make the careful observations Dr. Lander has demonstrated. I am in agreement with Dr. Boyle that these nephrotic children should not be overtreated, and that their management should be as simple as possible.

Our observations on this series are essentially in agreement with those in most other reported studies. All patients showed immediate remission of symptoms in varying degrees during the course of the measles infection. Some have remained

well during the period of observation; others have had relapses, and others have sustained varying degrees of improvement.

Although these patients were under close observation before, during and after their episode of measles, particularly with regard to biochemical studies of blood proteins and lipids, we could draw no conclusions as to the mechanism of the remission caused by measles. The increase in the gamma globulin fraction in some of the patients may be a reflection of their improved status and not necessarily the cause of the improvement. However, the role of the various globulin fractions, particularly the gamma globulin, merits investigation. We have treated several patients with large doses of gamma globulin over a prolonged period with no demonstrable effect.

The presence or absence of hematuria did not appear to have any prognostic significance in these patients. It has been our experience that practically all of them show bouts of hematuria. The degree of fever could not be correlated with the clinical response, and it is the usual experience that the ordinary febrile illnesses or artificially produced fevers do not cause remissions in this disease. It is common experience that febrile respiratory infections cause relapse.

We have observed remissions in other patients following severe pneumonia and peritonitis and, occasionally, in those who have had no acute infections.

It is impressive that an apparently hopelessly ill child, after acquiring a severe infectious disease, measles, can make such a remarkable and rapid improvement, even to the extent of having normal urine. We must conclude that the underlying pathologic lesion and pathophysiologic pattern may be reversible and that the prognosis of this condition is essentially hopeful.

In considering the therapeutic use of measles infection, one must consider the risk. In our series, while we had no mortality, we almost lost 1 patient with pneumonia, this patient being the one who showed the poorest end result. The use of gamma globulin or convalescent serum to modify the measles is probably advisable. We must also point out that we are not at all sure that any of our patients are cured and that prolonged observation will be necessary to determine this. Moreover, we cannot be certain that some of these patients would not have had spontaneous remissions sooner or later without measles.

Brief Report on Sampling of Certain Opinions of Local Pediatricians.
Dr. Gustave F. Weinfeld.

Recently the Chicago Association of Family Living asked for help in formulating its programs of parental instructions. Many of the mothers at these courses in parent-child relationships are attended by private pediatricians. In order to increase the value of the lay group teaching and so as not to confuse parents with conflicting or what we might consider unacceptable instruction, the association wanted to know the attitude of pediatricians toward certain problems.

My personal convictions would have been of small value. My impressions of the points of view of other pediatricians had no validity, for one remembers best, and is most impressed by, that which agrees with one's own thinking. Therefore, a limited, because of lack of time and funds, number of pediatricians were canvassed for their opinions. The questionnaire was reduced to a simple form at the expense of thoroughness to insure greater response. It was submitted to 50 pediatricians selected at random from our society. Forty-two completed questionnaires were returned.

Slide I, Feeding

A. Should babies be fed whenever they are hungry?
- Yes 35
- No 7

B. Should there be any specified limit of time between feedings?
- Yes 16
- No 22

C. Should babies be awakened to be fed?
- Yes 8
- No 32
- Immaterial 1
- Exceptions: Underweight, 10; last feeding, 3; over 5 hours, 3; others, 4.

D. Should the self-regulating diet be discarded at 3 months of age?
- Yes 16
- No 18

Slide II, Rooming-In

If facilities were available at your hospital, would you recommend rooming-in for selected mothers?
- Yes 31
- No 8

Slide III, Breast Feeding

A. Most important for health of infant 4
B. Most important for emotional satisfaction of infant 1
C. Most important for emotional satisfaction of mother 4
D. Equally important for emotional satisfaction of both 12
E. Unimportant in all respects 3
A and B 1
A and D 12
- 16 named health
- 20 did not name health
- 29 or 35 indicated some emotional factor

Almost all considered emotional factors important. About half expressed their opinion that health was also important. The wide variation in replies indicates the need for individualization by the pediatrician who best knows the mother and her infant.

Slide IV, Toilet Training

A. Do you recommend beginning at a definite chronologic age?
- Yes 9
  - Age, Mo.
  - 6 3
  - 8 to 9 1
  - 9 to 12 4
  - 18 1
- No 33

Only about 20 per cent specify a relatively early age.

Slide V, Toilet Training

Recommendations of those not specifying an early age for beginning training:

A. 15 employ physical signs, infant's rhythm or ability to sit.
B. 8 employ levels of socioemotional growth, the urge to be clean, expression, signal or normal neglect.
C. 6 recommend active intercession without any indications for doing so.
D. 4 gave no specific answer. (When the mother is insistent, a too early start delays ultimate training.)

None seem to object to delayed training. Most answers indicated importance of individualization. Apparently, it is easier and better to use physical rather than socioemotional indications. None mentioned the dangers of instituting training at too late an age.

Slide VI, Night Crying

A. Do you find this an important problem in the older infant?

Yes 23
No 17

B. Do you have a general interpretation and recommended technic for all cases of night crying?

Yes 13
No 21

Slide VII, Causes of Night Crying

What are some of the causes of this problem which you have encountered? (39 replies)

14, parental problems (such as overindulgence)
13, housing conditions (only cause in 2)
13, mentioned no emotional factors whatsoever
12, insecurity and fear in the infant
7, teething
6, demanding attention
5, clothing and room temperature
3, hunger
2, irritation by excreta
1, behavior is only cause
1, "majority are physical, minority are emotional"

One third did not mention emotional factors. In lay education greater stress should be placed on emotional factors, but emphasis should also be made on the need to consult the physician in ruling out contributing physical causes.

News and Comment

PERSONAL NEWS

Dr. Stuart S. Stevenson Given Research Professorship.—Dr. Stuart S. Stevenson, formerly assistant professor of child health at Harvard University, has accepted the appointment of research professor of pediatrics at the Children's Hospital, of Pittsburgh, and the University of Pittsburgh School of Medicine, effective Sept. 1, 1949.

Appointments Announced at Elizabeth Kenny Institute.—Dr. James F. Bosma, Minneapolis, assistant professor of pediatrics at University of Minnesota Medical School, and Dr. Bernard G. Lannin, St. Paul, in charge of orthopedics at the University of Minnesota Health Service, have become associated with the medical staff of Elizabeth Kenny Institute, in Minneapolis.

Announcement of the appointments was made by Dr. E. J. Huenekens, medical director of the Sister Elizabeth Kenny Foundation and chief of staff of Kenny Institute. Dr. Bosma will be in charge of pediatric service and Dr. Lannin of the orthopedic phases of care of patients with poliomyelitis at the institute.

Other members of the institute's medical staff are Dr. Miland E. Knapp, chief of physical medicine in charge of treatment and training, Dr. Myron Lecklitner, Dr. Theresa Haddy and Dr. R. E. Worden, associates in physical medicine, Dr. S. R. Seljeskog, chief of internal medicine and contagion, Dr. Lewis Sher, in charge of the outpatient department, and Dr. Wallace Cole and Dr. John F. Pohl, consulting orthopedists.

Service with National Foundation for Infantile Paralysis Announced.—Dr. Alex J. Steigman is currently serving as full time consultant in clinical epidemiology for The National Foundation for Infantile Paralysis, Inc., New York. Dr. Steigman's temporary departure from pediatrics is for the purpose of field work in early diagnosis, management and epidemiologic investigations of poliomyelitis. He has been associated with the pediatric departments at the University of Pennsylvania School of Medicine, Harvard Medical School and Temple University School of Medicine. Dr. Steigman recently completed a two year period as senior fellow in pediatrics, National Research Council, during which he conducted investigations in poliomyelitis at the Children's Hospital Research Foundation, in Cincinnati.

Book Reviews

Aureomycin—A New Antibiotic. By B. M. Duggar, M.D., and others. Annals of the New York Academy of Sciences, volume 51, article 4. Price, $2.50. Pp. 168, with many charts and graphs. New York: New York Academy of Sciences, 1948.

This is a collection of sixteen papers presented at a conference on aureomycin held by the Division of Mycology of the Section on Biology of the New York Academy of Sciences. The subject is covered intensively, from a general discussion of the discovery and source of aureomycin to the results of its use in various infections. The pharmacologic aspects and the toxicity of the drug are covered in detail, as are various bacteriologic studies in vitro and in vivo. Methods for determination of the antibiotic levels in body fluids are discussed.

Experimental work indicates that aureomycin is effective against a wide range of micro-organisms, including both bacilli and cocci. It appears also, on the basis of preliminary reports, to be highly effective against certain viral and rickettsial infections. Rocky Mountain spotted fever seems to be especially susceptible. California Q fever has responded promptly in a preliminary series of cases, and the drug has given indication of being specific for the virus of primary atypical pneumonia. Three cases of acute brucellosis showed bacteriologic and clinical remissions in seventy-two hours. Hodgkin's disease seems to be highly susceptible to aureomycin. Many other diseases have been treated with promising results. Only one tuberculous patient was included—a girl with draining sinuses of the neck for five years. After ten days' treatment, the drainage ceased and the glands were smaller. Treatment was continued for seven weeks. No follow-up study is reported. Experimentally, the drug seems to be highly effective in typhus.

In ocular infections, a wide range of conditions, including infections from both gram-positive and gram-negative bacilli and several viruses, are benefited.

Aureomycin may be given orally or intramuscularly. It appears to be just as effective orally, and most of the investigators recommend its use thus. Given intravenously in dogs it appears in the spinal fluid in therapeutic concentrations. Toxic effects seem to be rare and doses need not be large to produce results. It seemed to produce no resistant strains of organisms in experimental work and has proved effective in conditions resistant to penicillin and streptomycin.

This extensive collection of preliminary studies indicates that aureomycin may be an addition to the therapeutic armamentarium of the magnitude of penicillin.

Food Value Charts. No author given. Price, $1. No. of charts, 12. Philadelphia: The Philadelphia Child Health Society, 1948.

The set of 12 vitamin charts published by the Philadelphia Child Health Society depicts graphically the vitamin and mineral salt content of various foods. These should be useful in making up diets.

Technik der kinderärztlichen Differentialdiagnostik. By Dr. Alphons Solé. Price, 20 francs. Pp. 384, with 42 tables. Basel, Switzerland: Benno Schwabe & Co., 1948.

Much space is given to general inspection of a patient, with the formulation of various states, such as a pulmonary state or a cerebrospinal state. From such

states a "hypothesis of examination" is derived; that is, the general impression guides the examiner initially to a given organ or organ system. When such a hypothesis is not possible, a primary systematic examination is in order. Taking of a complete history is deferred and detailed directions are given for the anamnesis.

The second part of the book deals with the differential evaluation of symptoms. The fourth chapter discusses eruptions of the skin, the fifth, diseases of the skin. Unconsciousness and disturbances of consciousness are treated in the sixth chapter. Hemorrhages are the subject of the seventh chapter, and anemia that of the eighth. Chapter 9 is devoted to cyanosis, chapter 10 to disturbances of respiration. Vomiting and diarrhea each have separate chapters, 11 and 12, and so have spasms and paralysis, 13 and 14. In another chapter (15) icterus is the subject, and that of the sixteenth is edema. It should hardly be necessary to give directions how to take the temperature as in chapter 17, which considers several differential diagnostic points of fever. In chapter 18, typical kinds of facies are enumerated, such as facies atrophica, cardiaca, diptherotoxica, helminthica, luetica, malarica, mongoloides, morbiliosa, myxedematosa, peritonealic, pertussis, pneumonica, pylorica, scarletinosa, septica, scrofulotica, spasmophilica, tetanica and toxica—19 altogether. It is hardly necessary to mention that these descriptions of various facial types have to be taken with a grain of salt. At that, a hyperthyroid facies may be more clearly defined than some of the others.

The evaluation of the symptoms as given in these chapters is, on the whole, quite satisfactory. The systematic examination forms the subject of the third part of the book. The chapters deal with the examination of mouth and throat, bones and joints and the abdomen. The significance of an enlarged liver and an enlarged spleen is discussed in separate chapters. One chapter poses the question of failure of the infant to gain weight; another deals with the tuberculin reaction, and the last gives some pediatric data and measurements.

The subject matter of the various chapters is summarized in 21 tables (not 22 as stated on the title page). The reason these tables are given twice, once interspersed between the chapters and again at the end, is not clear.

Some few statements must be challenged, such as the statement that the most important symptom of true epilepsy is progressive decrease of intelligence and a peculiar change in character, and the statement that gallstones do not occur in childhood. Cyanosis is not a symptom of an open duct. Since a number of rare diseases have been omitted, probably intentionally, it is somewhat questionable whether thymic hypertrophy deserves any place. The omission of the anachronistic hodgepodge of morbus Benti might also be desirable. It is surprising that the significance of eyeground changes is not even mentioned.

The omission of such things as histoplasmosis and toxoplasmosis is understandable but detracts from the value of the book in this country. Dermatophytosis is not mentioned, nor is Meckel's diverticulum as a source of intestinal bleeding. In connection with Herter-Heubner (celiac) disease, fibrocystic disease of the pancreas demands recognition. Elevation of blood pressure due to one-sided renal aplasia with or without infection, though not frequent, might find a place, particularly since surgical treatment may be of greatest benefit. The good results of surgical treatment in some cases of congenital heart disease and coarctation of the aorta seem to justify consideration of the more important differential diagnostic points. A consideration of hepatic insufficiency may also not be amiss. The omission of glycogenosis (von Gierke's disease) from the storage diseases is to be corrected, and a consideration of enlargement of the liver in infants and children, in addition to histoplasmosis, galactosemia and steatosis, even though rare, should find a place.